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Total Synthesis and Revision of Absolute Stereochemistry of Antillatoxin, an Ichthyotoxic Cyclic Lipopeptide from Marine Cyanobacterium *Lyngbya majuscula*

Fumiaki Yokokawa, Hideyasu Fujiwara and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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Abstract—Antillatoxin is an ichthyotoxic cyclic lipopeptide isolated by Gerwick and co-workers from the marine cyanobacterium *Lyngbya majuscula* collected in Curaçao. Although we have finished the stereoselective total synthesis of antillatoxin having the proposed structure with (4*S*,5*R*)-configuration, we have found that the synthetic sample was not identical with the natural one and the proposed structure should be revised. Further our synthetic efforts have culminated in the first total synthesis of antillatoxin in its natural form, proving that the natural one has (4*R*,5*R*)-configuration.

Introduction

Marine cyanobacteria have proven to be exceptionally rich sources of structurally unique and biologically active natural products. Recently, Gerwick et al. reported their discovery and structural description of three distinct classes of structurally novel natural products from the marine cyanobacterium, *Lyngbya majuscula*, collected in Curaçao (Fig. 1). Curacin A was highly toxic to brine shrimp and also exhibited an antiproliferative activity due to its inhibition of tubulin polymerization.[1] Further studies of curacin A have established that it binds with high affinity to the colchicine site of tubulin and consequently inhibits the binding of colchicine.[2] This encouraging biological activity has motivated a significant world-wide effort towards the total synthesis of curacin A in a remarkably short time.[3] Barbamide was isolated from the same cyanobacterium by using snail bioassay and showed a strongly molluscicidal activity.[4] Its structure consists of a trichloromethyl portion and a thiazole amine portion, which appeared in dysidin[5] and dolastatin **10**,[6] respectively. In addition to curacin A and barbamide, a collection of *L. majuscula* furnished

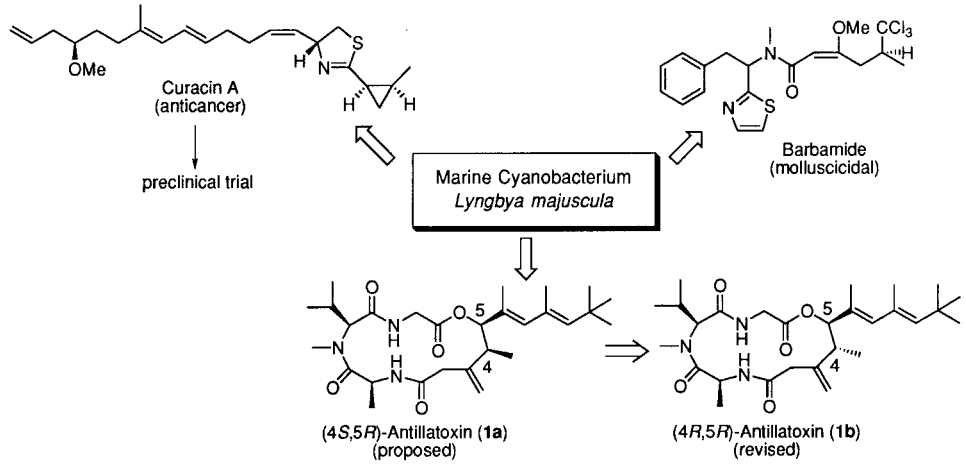

Figure 1. Natural products from the marine cyanobacterium *Lyngbya majuscula*.

Keywords: antillatoxin; ichthyotoxicity; cyclic lipopeptide; total synthesis.
* Corresponding author. Tel.: +81-52-836-3439; fax: +81-52-834-4172; e-mail: shioiri@phar.nagoya-cu.ac.jp

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the ichthyotoxic compound, antillatoxin.[7] Therefore, Gerwick et al. have speculated that this array of bioactive metabolites functions in nature protects this cyanobacterium from predation by crustacea, herbivorous fish and gastropod mollusks, which are abundant in the marine habitat in which this organism thrives.

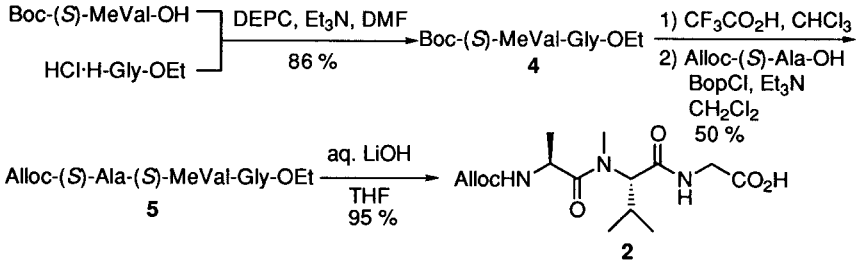
Antillatoxin (**1**) was isolated in low yield as an amorphous powder (1.3 mg, 0.07% of extract) from the ichthyotoxic crude extract of this marine cyanobacteria.[7] The gross structure of **1** was established using extensive NMR studies including COSY, LR COSY, and HMBC. The absolute stereochemistries of antillatoxin-derived *N*-methylvaline and alanine were determined by acid hydrolysis of **1**, HPLC separation and by chiral phase TLC versus standards. Both amino acids were present only as the l configuration. The stereochemistry at C4 and C5 was investigated using a combination of NOESY data, *J* values, CD spectroscopy and molecular modeling. Thus, the absolute stereochemistry at C4 and C5 was assigned as 4*S*,5*R* configuration, which was the lowest energy conformation in the modeling result. Antillatoxin is a structurally novel lipopeptide with a high degree of methylation. Especially, it has a conjugated diene that contains a *tert*-butyl group and a terminal olefin. In addition, a *cis* amide bond between alanine and *N*-methylvaline appears in the cyclic skeleton as a single rotational isomer. Goldfish toxicity measurements with antillatoxin showed it to be among the most ichthyotoxic metabolites isolated to date from a marine plant (LD_{50}=0.05 μg ml^{-1}), and it is exceeded in potency only by the brevetoxins (BTX-A LD_{50}=0.003 μg ml^{-1}). Antillatoxin is a structurally and biologically attractive marine natural product. As a part of our program toward the synthesis of biologically active peptides from marine origin,[8] we have embarked on the total synthesis of antillatoxin.[9] In this paper, we wish to disclose the full details of our synthetic efforts toward antillatoxin, which includes a revision of the absolute chemistry at C4 and C5.[10,11]

Synthetic strategy

Our convergent synthetic strategy to (4*S*,5*R*)-antillatoxin (**1a**), having the proposed structure, is shown in Fig. 2. As we believed that the isolated terminal olefin of antillatoxin would be easily isomerized, we first employed the use of the phenylselenomethyl group as a precursor of this olefin and postponed the oxidative elimination of the phenylselenyl group to the final stages of the synthesis. Therefore, antillatoxin would be constructed from two subunits, a tripeptide unit **2** and a diene fragment **3**. Segment condensation of these fragments followed by final macrolactamization would give the desired macrocycle.

Synthesis of the tripeptide unit

Preparation of the tripeptide unit **2** of antillatoxin was achieved in a stepwise manner from glycine ethyl ester, as shown in Scheme 1. Coupling of (*S*)-Boc-*N*-methylvaline with glycine ethyl ester was carried out using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[12] to give the dipeptide **4** in 86% yield. After removal of the Boc group from **4** with trifluoroacetic acid (TFA), the amine was condensed using bis (2-oxo-3-oxazolidinyl)phosphonic chloride (BopCl)[13] as the coupling reagent with allyloxycarbonyl (Alloc)-protected alanine in 50% yield. The resulting tripeptide **5** was saponified to furnish the tripeptide unit **2**, which was one partner for the upcoming fragment condensation.



Scheme 1.

Synthesis of the conjugated diene portion

We initially attempted the iterative Horner–Emmons protocol for the construction of the conjugated diene of antillatoxin. Pivalaldehyde **6** reacted with the phosphonate **7** to give the *E* isomer of **8** as the major product (*E*/*Z*>20:1) in 59% yield. In this reaction, no *E*/*Z* selectively was found using ethoxy analog **7′** in place of **7**. The ester **8** was then

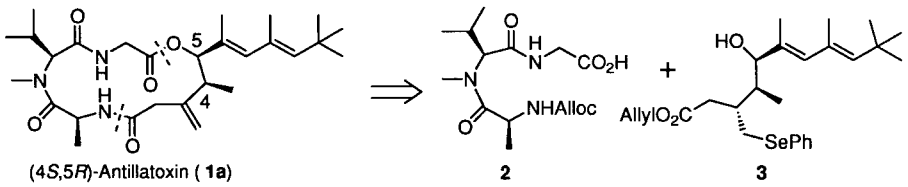
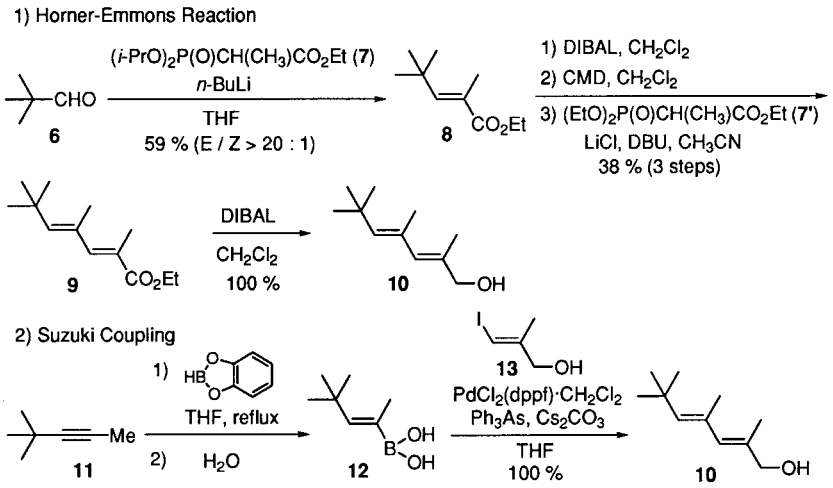


Figure 2. Retrosynthetic analysis of antillatoxin.



Scheme 2.

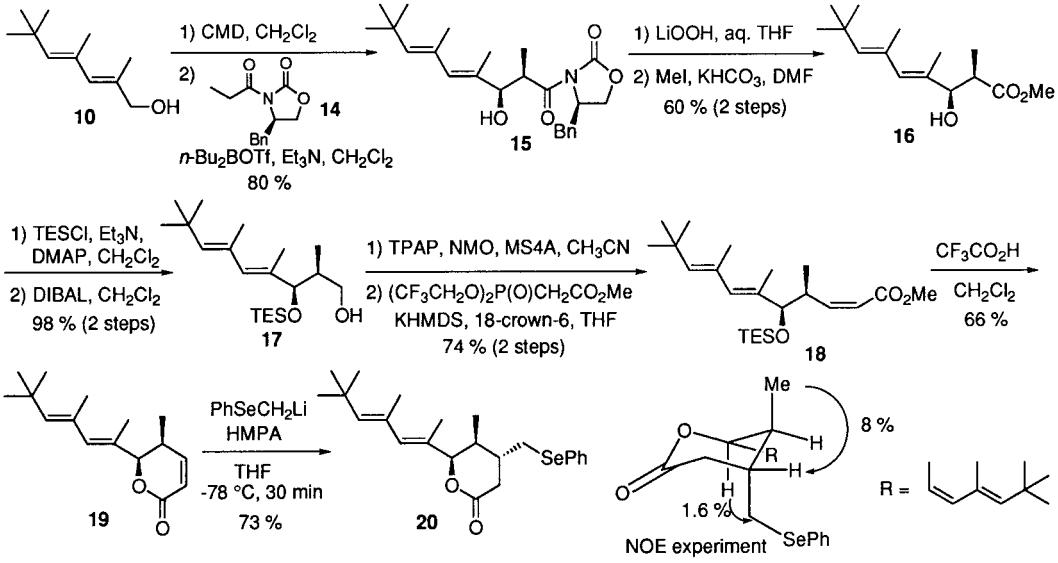
reduced with diisobutylaluminum hydride (DIBAL), and the allylic alcohol oxidized using chemical manganese dioxide (CMD)[14] to afford the corresponding aldehyde. A second Horner–Emmons condensation of this aldehyde with the phosphonate **7′** was carried out under the Masamune–Roush conditions[15] to give the conjugated diene **9** in 38% yield. Reduction of the conjugated ester **9** using DIBAL was carried out again to produce the desired alcohol **10** quantitatively.

As an improved route to the diene portion, the Suzuki coupling approach[16] was employed. This approach began from 4,4-dimethyl-2-pentyne (**11**),[17] which underwent the hydroboration with catecholborane followed by hydrolysis to give the vinylboronic acid **12**. This intermediate **12** was subjected to the Suzuki coupling with the known iodoalkene **13**[18] in the presence of a palladium catalyst, arsine ligand and cesium carbonate to afford the dienyl alcohol **10** quantitatively in a single operation (Scheme 2).

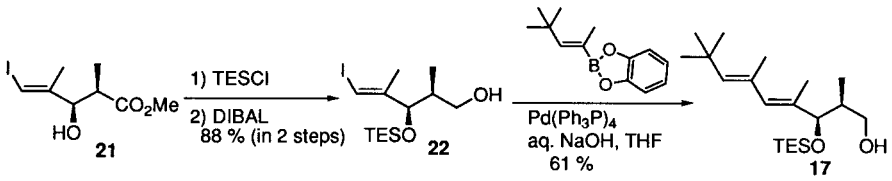
Synthesis of (4*S*,5*R*)-antillatoxin (proposed structure)

For construction of the *cis* configuration at C4, C5 in the proposed structure by Gerwick et al., a *syn* selective asymmetric aldol reaction by the methodology of Evans[19] was employed, as shown in Scheme 3.

Oxidation of the allylic alcohol **10** using CMD yielded the aldehyde, which was added to the boron enolate derived from the carboximide **14** to afford the corresponding aldol adduct **15** in good yield. Removal of the chiral auxiliary from **15** with alkaline hydrogen peroxide followed by methylation of the resulting carboxylic acid produced the methyl ester **16** in 60% yield. Protection of the secondary hydroxyl group of **16** as the triethylsilyl (TES) derivative and reduction of the methyl ester with DIBAL provided the primary alcohol **17** in 98% yield. Alternatively, the known hydroxy ester **21** prepared by the method of Baker[18] could also be transformed into the alcohol **17** in three steps. The



Scheme 3.



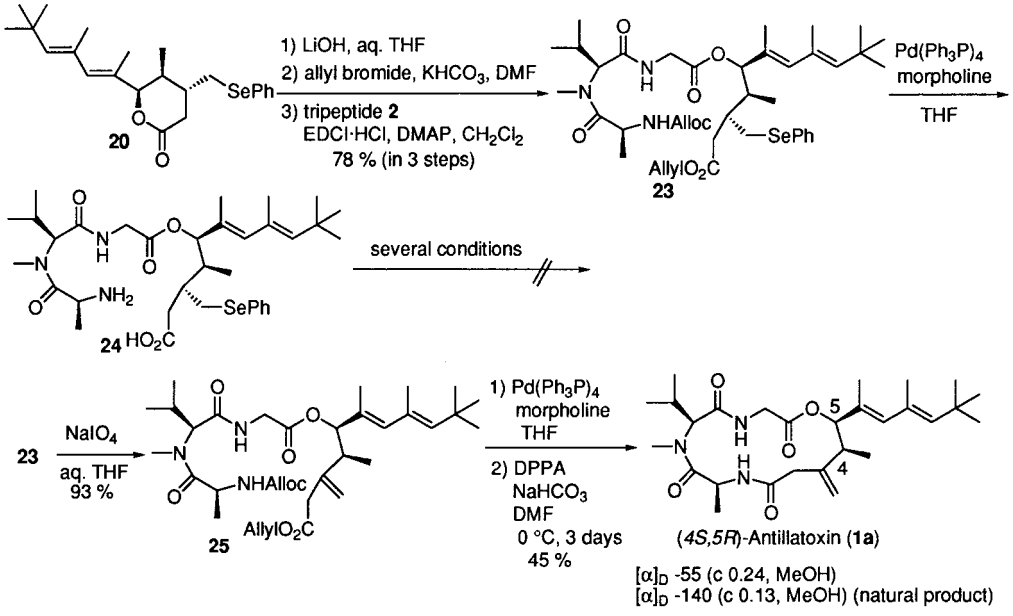
Scheme 4.

stereochemistry of the alcohol **17** prepared using the Evans aldol methodology was also confirmed by this alternative approach (Scheme 4).

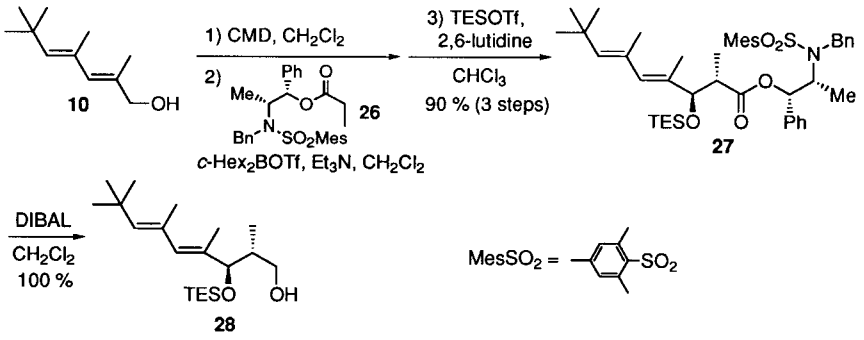
The alcohol **17** was then oxidized with tetrapropylammonium perruthenate (TPAP)[20] and this followed by a Still–Horner olefination[21] to afford the (*Z*)-ester **18** in 74% yield. Although the susceptibility of the dienyl hydroxyl moiety toward dehydration under the acidic condition was observed, careful treatment of **18** with TFA caused the cleavage of the secondary TES ether and the acid-catalyzed lactonization simultaneously to give the lactone **19** in moderate yield. Stereoselective introduction of the phenylselenomethyl group (as a precursor for the isolated terminal olefin) to the α,β-unsaturated lactone **19** was accomplished using $PhSeCH_2Li$ in the presence of HMPA[22] to provide the selenolactone **20** in 73% yield as a single isomer. The stereochemistry of **20** was assigned by NOE experiments, as shown in Scheme 3.

Saponification of the lactone ring in **20**, protection of the resulting carboxylic acid as the allyl ester, and segment condensation with the tripeptide unit **2** using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) gave the ester **23** in 78% yield. Treatment of **23** with $Pd(Ph_3P)_4$ in the presence of morpholine caused simultaneous removal of the *C*-terminal allyl group and the *N*-terminal allyloxy carbonyl group. However, final macrolactamization of the liberated amino acid **24** using several reagents led to decomposition of the starting material.[23] Accordingly, we attempted the macrolactamization after elimination of the phenylselenyl group. Oxidative elimination of the phenylselenyl group of **23** proceeded with $NaIO_4$ to provide the terminal olefin **25** in 93% yield. After removal of the protective groups, the resulting free amino acid could be cyclized under high dilution conditions using diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[24] and sodium hydrogen carbonate to produce (4*S*,4*R*)-antillatoxin (**1a**) in 45% yield (Scheme 5).

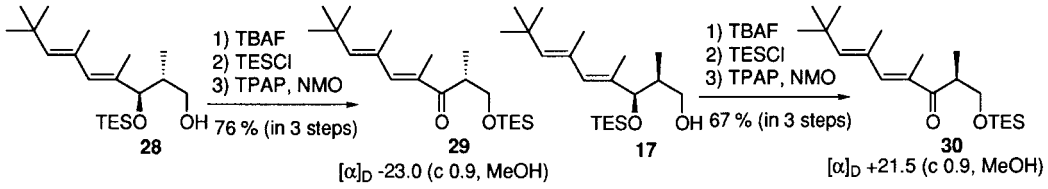
Although our synthetic (4*S*,5*R*)-antillatoxin showed reasonable ^1H and ^{13}C NMR spectra and HRMS (EI, obsd M^+ *m/z* 503.3362, 0.5 ppm error for $C_{28}H_{45}N_3O_5$), its NMR spectra showed significant differences from those of the natural product. Furthermore, the optical rotation of the synthetic sample ($[\alpha]_D=-55$ (*c* 0.24, MeOH)) was also different from that of the natural product ($[\alpha]_D=-140$ (*c* 0.13, MeOH)). These differences led us to the conclusion that the formula **1a** does not accurately reflect the stereostructure for antillatoxin. On the basis of the assumption that the stereochemistries of amino acids are secure, we supposed that the stereochemistry at C4 and C5 would be misassigned. After the completion of our synthesis, White et al. also have accomplished the total synthesis of (4*S*,5*R*)-antillatoxin (**1a**) and reached to the same conclusion as ours independently.[11a] Unfortunately, the amount of natural



Scheme 5.



Scheme 6.



Scheme 7.

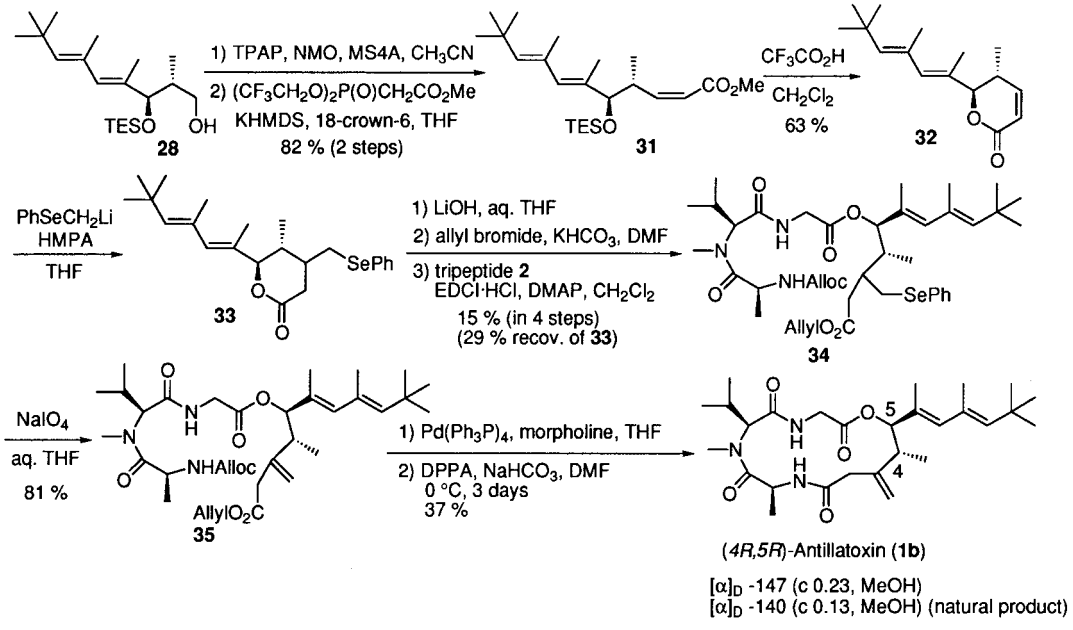
antillatoxin was very minute, and firm assignment of structure by a method other than synthesis might be difficult at this time.

Synthesis of (4*R*,5*R*)-antillatoxin (revised structure)

Next, we focused our attention on the synthesis of (4*R*,5*R*)-antillatoxin, which was proposed as the second possible configuration by Gerwick et al.[7] For the construction of the anti-C4, C5 configuration, we intended to use the anti-selective boron-mediated asymmetric aldol reaction developed by Abiko and Masamune.[25] After oxidation of alcohol **10**, the resulting aldehyde was added to the *E*-enolate solution, which was generated from the propionate ester of norephedrine derivative using dicyclohexylboron triflate and triethylamine. Subsequently, protection of the secondary alcohol gave the anti-aldol adduct **27**, which was converted to the corresponding alcohol **28** using DIBAL reduction (Scheme 6).

The absolute stereochemistry of chiral alcohol **28** was confirmed by comparison of the optical rotation data of the corresponding ketone **29** with **30**, which was derived from the already stereochemically evident alcohol **17** (Scheme 7).

The alcohol **28** was transformed into (4*R*,5*R*)-antillatoxin (**1b**) in the same way as developed in the synthesis of



Scheme 8.

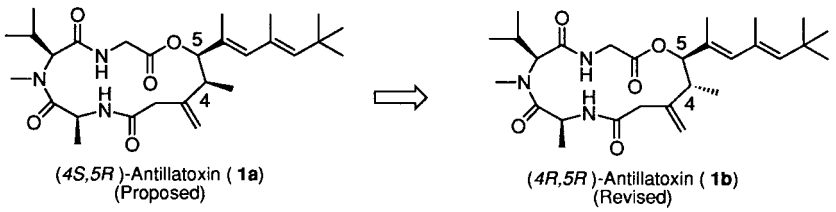


Figure 3. Revision of the proposed structure of antillatoxin.

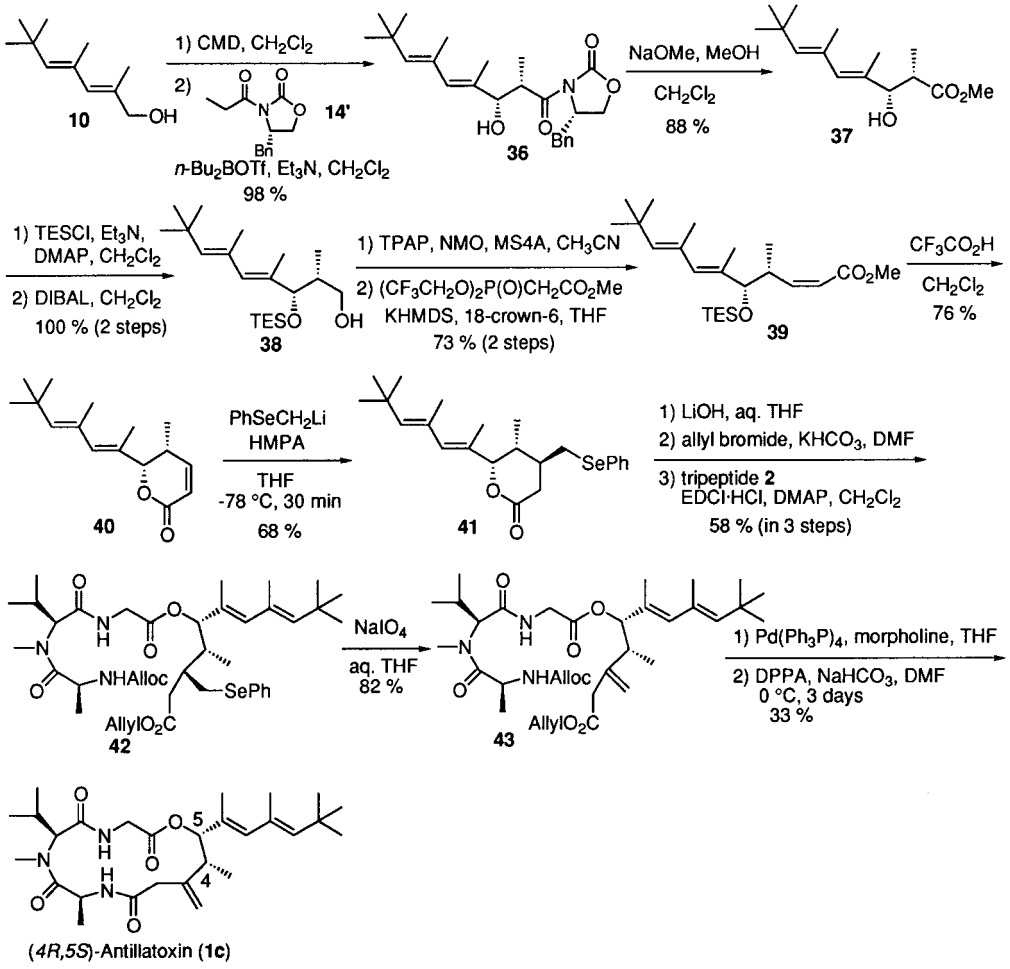
(4*S*,5*R*)-antillatoxin (**1a**). Thus, the TPAP oxidation of **28** and Still's olefination gave the α,β-unsaturated ester **31**, which was treated with TFA to afford the α,β-unsaturated lactone **32**. Although the lactone **32** could be transformed into the phenylselenyl derivative **33**, no stereoselectivity was observed in this 1,4-addition. Alkaline hydrolysis of **33**, allyl esterification, and coupling with the tripeptide unit **2** produced the ester **34**, which underwent the oxidation to give the linear precursor **35**. Deprotection at the *N*- and *C*-terminals followed by macrolactamization with DPPA finally afforded (4*R*,5*R*)-antillatoxin (**1b**) (Scheme 8).

The synthetic (4*R*,5*R*)-antillatoxin (**1b**) was found to be identical to the natural antillatoxin by comparison of their ^{1}H NMR, ^{13}C NMR and IR. The optical rotation of our synthetic sample ($[\alpha]_D=-147$ (*c* 0.23, MeOH)) also matched that of the natural product ($[\alpha]_D=-140$ (*c* 0.13, MeOH)). Accordingly, these results indicate that the real structure of antillatoxin has (4*R*,5*R*)-configuration.

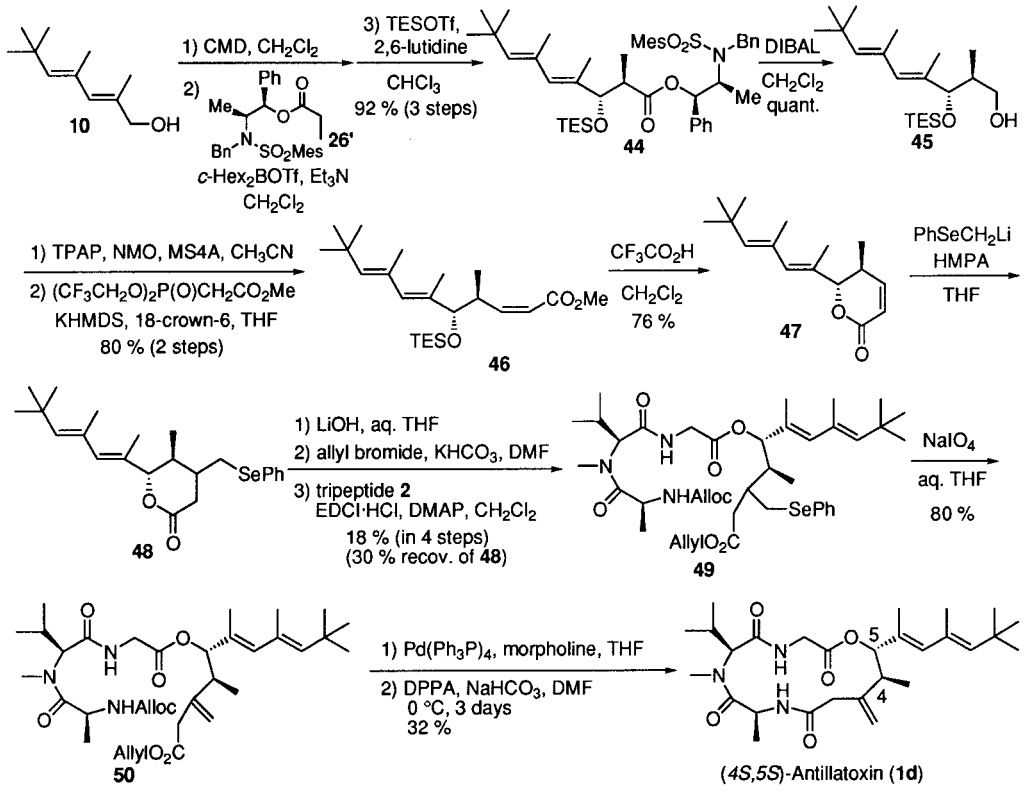
Conclusion

In conclusion, we achieved the total synthesis of (4*S*,5*R*)- and (4*R*,5*R*)-antillatoxins in an enantioselective convergent manner using Evans and Abiko–Masamune asymmetric aldol reactions, respectively. Our total synthesis indicates that the structure assigned to antillatoxin must be revised to the (4*R*,5*R*)-configuration (Fig. 3).

Furthermore, we have also accomplished the total synthesis of (4*R*,5*S*)- and (4*S*,5*S*)-antillatoxins by a common strategy which uses antipodal aldol reactions (Scheme 9 and Scheme



Scheme 9.



Scheme 10.

10). Biological and pharmacological evaluation of our synthetic four isomers of antillatoxin are currently underway.

Experimental

General information

Melting points were measured with a YANACO melting point apparatus (hot plate) and are uncorrected. Infrared spectra were recorded on a JASCO IRA-2 or SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a JASCO DIP-140 or DIP-1000 digital polarimeters with a sodium lump (λ=589 nm, D line) and are reported as follows: $[\alpha]_D^T$=(c g/100 ml, solvent).

^{1}H NMR spectra were recorded on a JEOL EX-270 (270 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. Antillatoxin numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm).

Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Preparative thin layer chromatography was performed on Merck Art. 5744, Kiselgel 60F_{254}/0.5 mm thickness plates. Elementary analysis (Anal) and high-resolution mass spectra (HRMS) were done at the Analytical Facility at Nagoya City University.

Solvents for extraction and chromatography were reagent grade. Liquid chromatography was performed with forced flow (flash chromatography of the indicated solvent mixture on silica gel BW-820MH or BW-200 (Fuji Davison Co.)). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Acetonitrile (CH_3CN) and *N*,*N*-dimethylformamide (DMF) were dried over 4 Å molecular sieves. Triethylamine was dried over potassium hydroxide. All other commercially available reagents were used as received.

Boc-(*S*)-Me-Val-Gly-OEt (4). To a solution of Boc-(*S*)-Me-Val-OH (2.07 g, 8.96 mmol) and HCl·H-Gly-OEt (1.31 g, 9.39 mmol) in DMF (20 ml) was successively added dropwise DEPC (1.5 ml, 9.89 mmol) and triethylamine (3.1 ml, 22.2 mmol). After being stirred at 0°C for 2 h and then at room temperature for 3 h, the reaction mixture was diluted with ether and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane–EtOAc=3:1) to

afford the desired product **4** as a colorless oil (2.444 g, 86%): $[\alpha]_D^{26}=-117.7$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3337, 1755, 1682, 1679, 1526, 1480, 1445, 1393, 1368, 1196, 1157; ^1H NMR ($CDCl_3$) δ 0.87 (3H, d, *J*=6.9 Hz, Val-C*H*$_3$), 0.96 (3H, d, *J*=6.3 Hz, Val-C*H*$_3$), 1.27 (3H, t, *J*=6.9 Hz, CH_2CH_3), 2.28 (1H, m, Val-$(CH_3)_2$CH), 1.48 (9H, s, *t-Bu*), 2.80 (3H, s, N-C*H*$_3$), 4.00 (2H, d, *J*=5.6 Hz, Gly-C*H*$_2$), 4.19 (3H, m, Val-α-H, C*H*$_2$CH$_3$), 6.65 (1H, br, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.4, 19.6, 26.0, 26.2, 28.3, 30.0, 41.0, 61.1, 64.1, 156.9, 169.4, 170.9. Anal. Calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.75; H, 8.99; N, 8.71.

Alloc-(*S*)-Ala-(*S*)-Me-Val-Gly-OEt (5). The dipeptide **4** (503 mg, 1.59 mmol) was dissolved in $CHCl_3$ (2 ml), and TFA (2 ml) was added at room temperature. The solution was stirred for 20 min and concentrated. The residue was azeotropically concentrated with toluene (×2). The resulting residue and Alloc-(*S*)-Ala-OH (275 mg, 1.59 mmol) were dissolved in CH_2Cl_2 (5.3 ml) and cooled to 0°C. BopCl (445 mg, 1.75 mmol) and triethylamine (0.67 ml, 4.8 mmol) were successively added, and the mixture was stirred at 0°C for 18 h. After dilution with EtOAc, the mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=3:2) to afford the desired product **5** as a colorless oil (294 mg, 50%): $[\alpha]_D^{26}=-139.7$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3316, 1723, 1684, 1638, 1530, 1464, 1244, 1200; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-C*H*$_3$), 0.98 (3H, d, *J*=6.3 Hz, Val-C*H*$_3$) 1.26 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.35 (3H, d, *J*=6.6 Hz, Ala-C*H*$_3$), 2.33 (1H, m, Val-$(CH_3)_2$C*H*), 3.03 (3H, s, N-C*H*$_3$), 3.83 (1H, dd, *J*=17.8, 5.3 Hz, Gly-C*H*$_2$), 4.08 (1H, dd, *J*=17.8, 6.6 Hz, Gly-C*H*$_2$), 4.18 (2H, q, *J*=7.3 Hz, C*H*$_2$CH$_3$), 4.53 (3H, m, CH_2=CHC*H*$_2$, Val-α-*H*), 4.68 (1H, m, Ala-α-*H*), 5.34-5.19 (2H, m, C*H*$_2$=CHCH$_2$), 5.66 (1H, d, *J*=7.6 Hz, Ala-N*H*), 5.98–5.80 (1H, m, CH_2=C*H*CH$_2$), 6.55 (1H, br, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.4, 19.4, 25.5, 30.4, 40.9, 47.1, 61.2, 62.4, 65.5, 117.5, 132.7, 155.4, 169.5, 170.1, 174.0. HRMS (EI) *m/z* Calcd for $C_{17}H_{29}N_3O_6$: 371.2056. Found: 371.2055.

Alloc-(*S*)-Ala-(*S*)-Me-Val-Gly-OH (2). To a solution of the tripeptide **5** (270 mg, 0.71 mmol) in THF (2 ml) at 0°C was added a solution of LiOH (60 mg) in water (2 ml). The resulting mixture was stirred at 0°C for 10 min. After dilution with water, the mixture was washed with ether. The aqueous layer was acidified to pH 3 by the addition of 1 M aqueous $KHSO_4$ and salted out. The mixture was extracted with ether (×3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford the desired product **2** as a colorless viscous oil (238 mg, 95%): $[\alpha]_D^{25}=-151.0$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3316, 1720, 1682, 1636, 1588, 1470, 1414, 1246, 1065; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-C*H*$_3$), 0.97 (3H, d, *J*=6.6 Hz, Val-C*H*$_3$), 1.30 (3H, d, *J*=6.9 Hz, Ala-C*H*$_3$), 2.31 (1H, m, Val-$(CH_3)_2$C*H*), 3.03 (3H, s, N-C*H*$_3$), 3.94 (1H, m, Val-α-*H*), 4.11 (1H, m, Ala-α-*H*), 4.56 (2H, d, *J*=5.6 Hz, CH_2=CHC*H*$_2$), 4.65 (2H, d, *J*=11.2 Hz, Gly-C*H*$_2$), 5.23 (2H, m, C*H*$_2$=CHCH$_2$), 5.80–5.40 (1H, br, CO_2H), 5.85 (1H, m, CH_2=C*H*CH$_2$), 6.94 (1H, br, Gly-N*H*), 6.94 (1H, d, *J*=8.3 Hz, Ala-N*H*); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.5, 19.4, 25.7, 30.6, 40.9, 47.3, 62.8, 65.8, 117.8, 132.7, 155.7, 170.2, 172.3, 174.7. HRMS (EI) *m/z* Calcd for $C_{15}H_{25}N_3O_6$: 343.1743. Found: 343.1743.

Ethyl (2*E*)-2,4,4-trimethyl-2-pentenoate (8). To a solution of the phosphonate **7** (2.7 g, 10.1 mmol) in THF (30 ml) at −20°C was added *n*-BuLi (1.68 mol l^{-1} in hexane, 6 ml, 10.1 mmol). After being stirred at −20°C for 30 min, to the resulting solution was added pivaladehyde (1 ml, 9.21 mmol) by syringe. The reaction mixture was stirred at −20°C for 1 h and then at room temperature for 9.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with brine, dried ($MgSO_4$), filtered and concentrated. The residue was distilled to afford **8** (922 mg, 59%) as a colorless oil, which was used for the next step without further purification: bp 120°C/25 mmHg (Kugelrohr); IR ν_{max}^{neat} cm^{-1} 1711, 1644, 1466, 1366, 1281, 1250, 1200, 1109; ^1H NMR ($CDCl_3$) δ 1.18 (9H, s, *t-Bu*), 1.29 (3H, t, *J*=6.9 Hz, CH_2CH_3), 1.95 (3H, d, *J*=1.3 Hz, C_{15}-C*H*$_3$), 4.18 (2H, q, *J*=6.9 Hz, C*H*$_2$CH$_3$), 6.79 (1H, q, *J*=1.3 Hz, C_9-*H*); ^{13}C NMR ($CDCl_3$) δ 13.1, 14.1, 29.9, 32.8, 60.4, 126.5, 150.9, 169.1.

Ethyl (2*E*,4*E*)-2,4,6,6-tetramethyl-2,4-heptadienoate (9). To a solution of the ester **8** (705 mg, 4.14 mmol) in CH_2Cl_2 (10 ml) at −78°C was added DIBAL (0.95 mol/l in hexane, 13 ml, 12.35 mmol) dropwise. The resulting solution was stirred at −78°C for 50 min and quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with ether (×1). The organic extracts were washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the alcohol (631 mg) as a colorless oil, which was used for the next step without further purification.

To a solution of the alcohol (631 mg) in CH_2Cl_2 (11 ml) was added CMD (3 g, 34.5 mmol) in one portion. After being stirred at room temperature for 2.5 h, an additional CMD (3 g, 34.5 mmol) was added. After stirring for an additional 3.5 h, an additional CMD (2.5 g, 28.8 mmol) was added. The mixture was stirred for an additional 11 h, and CMD was removed by filtration through a Celite and washed with ether. The resulting filtrate was concentrated to afford the aldehyde (604 mg) as a colorless oil, which was used for the next step without further purification.

To a suspension of LiCl (218 mg, 5.14 mmol) in CH_3CN (6 ml) were subsequently added the phosphonate **7′** (1.1 ml, 5.13 mmol) and DBU (0.7 ml, 4.68 mmol). After being stirred at room temperature for 5 min, to the resulting solution was added the above aldehyde in CH_3CN (2 ml, plus 2 ml rinse) by cannula. The mixture was stirred at room temperature for 8 h, and the bulk of solvent was removed. The residue was diluted with ether, washed with saturated NH_4Cl, water and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. Silica gel column chromatography (BW-820MH, hexane–ether=60:1) afforded the diene **9** as a colorless oil (330 mg, 38%). A small amount of the sample was purified for analysis by distillation (bp 130°C/10 mmHg, Kugelrohr): IR ν_{max}^{neat} cm^{-1}

1709, 1624, 1466, 1447, 1366, 1254, 1223, 1113; ^{1}H NMR ($CDCl_3$) δ 1.16 (9H, s, *t-Bu*), 1.30 (3H, t, J=6.9 Hz, CH_2CH_3), 1.91 (3H, d, J=1.3 Hz, C_{14}-CH_3) 1.97 (3H, d, J=1.3 Hz, C_{15}-CH_3), 4.20 (2H, q, J=6.9 Hz, CH_2CH_3), 5.56 (1H, br, C_9-*H*), 7.08 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.2, 17.2, 30.6, 32.9, 60.4, 125.1, 130.8, 144.8, 145.2, 169.1. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.21; H, 10.68.

(2*E*,4*E*)-2,4,6,6-tetramethyl-2,4-heptadienol (10). *By DIBAL reduction:* To a solution of the ester **8** (281 mg, 4.14 mmol) in CH_2Cl_2 (10 ml) at −78°C was added DIBAL (1.5 mol l^{-1} in toluene, 2.7 ml, 4.05 mmol) dropwise. The resulting solution was stirred at −78°C for 25 min and quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane–ether=5:1) to afford the alcohol **10** as colorless oil (235 mg, quant.).

By Suzuki coupling: **4, 4-Dimethyl-2-pentyne (11)** (1.44 g, 15 mmol) was dissolved in THF (20 ml) and catecholborane (1 M in THF, 15 ml, 15 mmol) was added. The mixture was heated to reflux for 1 h, washed with H_2O, and concentrated. The residue was diluted with THF (20 ml) and a solution of vinyl iodide **13** (1.39 g, 7 mmol) in THF (3 ml) was added. To this solution was added Cs_2CO_3 (4.56 g, 14 mmol), $PdCl_2$ (dppf)$_2$·CH_2Cl_2 (143 mg, 0.175 mmol) and $AsPh_3$ (107 mg, 0.35 mmol). After being stirred for 24 h at room temperature, the mixture was filtered through celite pad, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane–ether=5:1) to afford the desired product **10** as a colorless oil (1.178 g, quant.): IR ν_{max}^{neat} cm^{-1} 3339, 1466, 1445, 1362, 1071, 1009; ^{1}H NMR ($CDCl_3$) δ 1.14 (9H, s, *t-Bu*), 1.77 (3H, d, J=1.7 Hz, C_{14}-CH_3), 1.82 (3H, d, J=1.3 Hz, C_{15}-CH_3), 2.53 (1H, br, O*H*), 3.99 (2H, br, CH_2), 5.31 (1H, s, C_9-*H*), 5.84 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 15.0, 17.8, 30.9, 32.4, 69.0, 130.8, 131.1, 133.7, 140.2. HRMS (EI) *m*/*z* Calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1487.

[4*R*,3(2*R*,3*R*)]-4-Benzyl-3-(3-hydroxy-2,4,6,8,8-pentamethyl-4,6-nonadienoyl)-2-oxazolidinone (15). To a solution of the alcohol **10** (644 mg, 3.83 mmol) in CH_2Cl_2 (11 ml) was added CMD (5.7 g, 65.6 mmol) in one portion. The mixture was stirred at room temperature for 4 h, and CMD was removed by filtration through a pad of celite and washed with ether. The resulting filtrate was concentrated to afford the aldehyde.

To a solution of propionyl oxazolidinone **14** (893 mg, 3.83 mmol) in CH_2Cl_2 (8 ml) at 0°C were added dropwise dibutylboryl triflate (1.14 ml, 4.53 mmol) and triethylamine (0.71 ml, 5.09 mmol) at a rate such that the internal temperature stayed below 3°C. The resulting clear, colorless solution was cooled to −78°C, and a solution of the above aldehyde in CH_2Cl_2 (1 ml, plus 1 ml rinse) was added by cannula. After 20 min, the solution was allowed to warm to −5°C for 40 min and quenched by the addition of the phosphate buffer (1.7 ml, pH 7) and methanol (4.8 ml). To this was added 2:1 methanol–30% aqueous H_2O_2 (3.9 ml) carefully so as to keep the internal temperature below 5°C. The volatiles were removed in vacuo and water was added. The mixture was extracted with ether (×1). The organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=6:1) to afford the desired product **15** as a yellow oil (1.429 g, 93%): $[\alpha]_D^{26}$=−21.3 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3538, 1782, 1700, 1455, 1381, 1362, 1210, 1107; ^{1}H NMR ($CDCl_3$) δ 1.14 (9H, S, *t-Bu*), 1.21 (3H, d, J=6.9 Hz, C_{13}-CH_3), 1.72 (3H, d, J=1.3 Hz, C_{14}-CH_3), 1.81 (3H, d, J=1.3 Hz, C_{15}-CH_3), 2.80 (1H, dd, J=13.2, 9.6 Hz, ArCH_2), 2.81 (1H, d, J=3.0 Hz, O*H*), 3.28 (1H, dd, J=13.5, 3.3 Hz, ArCH_2), 4.01 (1H, m, C_{13}-*H*), 4.21 (2H, m, CH_2O), 4.37 (1H, br, C_5-*H*), 4.67 (1H, m, C*H*N), 5.28 (1H, s, C_9-*H*), 5.99 (1H, s, C_7-*H*), 7.34–7.20 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.6, 14.8, 18.0, 30.9, 32.5, 37.7, 40.5, 55.2, 66.1, 75.6, 127.3, 128.9, 129.3, 130.8, 131.6, 132.6, 135.0, 140.1, 152.9, 177.0. HRMS (EI) *m*/*z* Calcd for $C_{24}H_{33}NO_4$: 399.2409. Found: 399.2401.

Methyl (2*R*,3*R*,4*E*,6*E*)-3-hydroxy-2,4,6,8,8-pentamethyl-4,6-nonadienoate (16). To a solution of the aldol adduct **15** (1.429 g, 3.58 mmol) in THF–water (4:1, 8 ml) was added 30% aqueous H_2O_2 (1.45 ml, 14.3 mmol), followed by the addition of a solution of LiOH (240 mg, 5.72 mmol) in water (5.9 ml) at 0°C. After the solution was stirred for 25 min, sodium sulfite (1.8 g, 14.3 mmol) in water (10 ml) was added. The mixture was washed with ether, and the aqueous layer was acidified to pH 3 by the addition of 1 M aqueous $KHSO_4$. The mixture was salted out, and extracted with ether (×3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford the hydroxy acid. The hydroxy acid was dissolved in DMF (5 ml), and $KHCO_3$ (657 mg, 6.56 mmol) was added, followed by the addition of methyl iodide (0.37 ml, 5.94 mmol). The mixture was stirred at room temperature for 18 h. After dilution with ether, the mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane–EtOAc(5:1) to afford the desired product **16** as a colorless oil (542 mg, 60%): $[\alpha]_D^{26}$=+8.7 (*c* 1.1, $CHCl_3$); IR $\nu_{max}^{neat}$$cm^{-1}$ 3496, 1740, 1456, 1435, 1362, 1256, 1200, 1165, 1038; ^{1}H NMR ($CDCl_3$) δ 1.14 (9H, s, *t-Bu*), 1.16 (3H, d, J=7.3 Hz, C_{13}-CH_3), 1.71 (3H, d, J=1.3 Hz, C_{14}-CH_3), 1.79 (3H, d, J=7.3 Hz, C_{15}-CH_3), 2.59 (1H, br, O*H*), 2.75 (1H, m, C_4-*H*), 3.67 (3H, s, CH_3 ester), 4.25 (1H, br, C_5-*H*), 5.26 (1H, t, J=1.3 Hz, C_9-*H*), 5.88 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 11.3, 13.8, 17.8, 30.9, 32.5, 43.1, 51.6, 76.5, 130.6, 132.2, 133.1, 140.1, 175.8. HRMS (EI) *m*/*z* Calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1882.

(2*S*,3*R*,4*E*,6*E*)-3-trimethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienol (17). To a solution of the alcohol **16** (524 mg, 2.13 mmol) in CH_2Cl_2 (7 ml) was added triethylamine (0.6 ml, 4.30 mmol), TESC1 (0.54 ml, 3.22 mmol) and DMAP (6 mg, 0.049 mmol) at 0°C. After being stirred at 0°C for 15 min and then at room temperature for 2.5 h, the mixture was diluted with ether. The mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous

$NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the silyl ether.

To a solution of the silyl ether in CH_2Cl_2 was added DIBAL (0.94 M in hexane, 6.8 ml, 6.39 mmol) at −78°C. After being stirred at −78°C for 10 min and then at 0°C for 20 min, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with ether (×1). The organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=6:1) to afford the desired product **17** as a colorless oil (712 mg, 98%): $[\alpha]_D^{25}$=+1.9 (*c* 1.1, MeOH); IR ν_{max}^{neat} cm^{-1} 3368, 1460, 1414, 1377, 1362, 1238, 1019; ^1H NMR ($CDCl_3$) δ 0.60 (6H, q, *J*=7.9 Hz, Si*CH*$_2$CH$_3$), 0.90 (3H, d, *J*=6.9 Hz, C_{13}-C*H*$_3$), 0.95 (9H, t, *J*=7.9 Hz, SiCH$_2$C*H*$_3$), 1.14 (9H, s, *t-Bu*), 1.71 (3H, d, *J*=1.3 Hz, C_{14}-C*H*$_3$), 1.79 (3H, d, *J*=1.3 Hz, C_{15}-C*H*$_3$), 1.88 (1H, m, C_4-*H*), 1.97 (1H, br, O*H*), 3.57–3.44 (2H, m, C_3-C*H*$_2$), 3.93 (1H, d, *J*=6.3 Hz, C_5-*H*), 5.24 (1H, t, *J*=1.3 Hz, C_9-*H*), 5.78 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 4.8, 6.8, 12.7, 13.9, 17.9, 31.0, 32.5, 39.8, 66.0, 80.8, 130.7, 132.1, 135.4, 139.8. Anal. Calcd for $C_{20}H_{40}O_2Si$: C, 70.52; H, 11.84. Found: C, 70.27; H, 12.12.

Methyl (4*S*,5*R*,2*Z*,6*E*,8*E*)-5-triethylsiloxy-4,6,8,10,10-pentamethyl-6,8-undecadienoate (18). To a stirred mixture of the alcohol **17** (525 mg, 1.54 mmol), *N*-methylmorpholine *N*-oxide (271 mg, 2.31 mmol) and powdered 4 Å molecular sieves (770 mg) in CH_3CN (6 ml) was added TPAP (27 mg, 0.077 mmol) in one portion at 0°C. After being stirred at 0°C for 5 min and then at room temperature for 20 min, the mixture was filtered through silica gel column and the filtrate was concentrated to afford the aldehyde.

A solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.65 ml, 3.07 mmol) and 18-crown-6 (1.93 g, 7.30 mmol) in THF (10 ml) was cooled to −78°C and treated with KHMDS (0.5 M in toluene, 5.8 ml, 2.9 mmol). A solution of the aldehyde in THF (2 ml, plus 2 ml rinse) was added by cannula and the resulting mixture was stirred at −78°C for 20 min and then at −10°C for 20 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with ether (×1). The organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–ether=50:1) to afford the desired product **18** as a colorless oil (449 mg, 74%): $[\alpha]_D^{26}$=+86.0 (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1727, 1646, 1460, 1437, 1408, 1379, 1362, 1237, 1196, 1177, 1073, 1009; ^1H NMR ($CDCl_3$) δ 0.57 (6H, q, *J*=8.3 Hz, Si*CH*$_2$CH$_3$), 0.94 (9H, t, *J*=8.3 Hz, SiCH$_2$C*H*$_3$), 1.01 (3H, d, *J*=6.6 Hz, C_{13}-C*H*$_3$), 1.13 (9H, s, *t-Bu*), 1.64 (3H, d, *J*=1.3 Hz, C_{14}-C*H*$_3$), 1.75 (3H, d, *J*=1.0 Hz, C_{15}-C*H*$_3$), 3.67 (1H, m, C_4-*H*), 3.71 (3H, s, C*H*$_3$ ester), 3.79 (1H, d, 6.9 Hz, C_5-*H*), 5.18 (1H, t, *J*=1.3 Hz, C_9-*H*), 5.68 (1H, dd, *J*=11.6, 0.7 Hz, C_2-*H*), 5.73 (1H, s, C_7-*H*), 6.02 (1H, dd, *J*=11.5, 10.6 Hz, C_3-*H*); ^{13}C NMR ($CDCl_3$) δ 4.9, 6.9, 13.2, 15.7, 17.8, 31.0, 32.5, 37.3, 51.0, 81.8, 117.7, 130.8, 131.7, 135.8, 139.6, 153.3, 166.7. Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73. Found: C, 69.93; H, 10.67.

(4*S*,5*R*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1,3-hexadienyl)-4-methyl-2-pentene-5-olide (19). To a solution of the ester **18** (449 mg, 1.14 mmol) in CH_2Cl_2 (7 ml) was added dropwise TFA (0.053 ml, 0.69 mmol) at −10°C. The mixture was slowly warmed to room temperature over 19 h, and then the additional TFA (0.015 ml, 0.20 mmol) was added. After stirring at room temperature for 3.5 h, the reaction mixture was quenched by the addition of triethylamine. After concentration of the mixture, the residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=5:1) to afford the desired product **19** as a colorless oil (187 mg, 66%): $[\alpha]_D^{25}$=+357.6 (*c* 0.3, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1728, 1453, 1381, 1372, 1246, 1107, 1065; ^1H NMR ($CDCl_3$) δ 0.96 (3H, d, *J*=7.3 Hz, C_{13}-C*H*$_3$), 1.15 (9H, s, *t-Bu*), 1.74 (3H, s, C_{14}-C*H*$_3$), 1.82 (3H, d, *J*=1.0 Hz, C_{15}-C*H*$_3$), 2.56 (1H, m, C_4-*H*), 4.80 (1H, br, C_5-*H*), 5.30 (1H, t, *J*=1.3 Hz, C_9-*H*), 6.00 (1H, d, *J*=9.6, C_2-*H*), 6.12 (1H, s, C_7-*H*), 7.02 (1H, dd, *J*=9.6 Hz, 6.3 Hz, C_3-*H*); ^{13}C NMR ($CDCl_3$) δ 11.6, 14.8, 17.7, 30.7, 31.6, 32.4, 82.1, 119.6, 127.9, 130.3, 131.9, 140.2, 151.7, 164.1. HRMS (EI) *m*/*z* Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1765.

(3*R*,4*S*,5*R*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1,3-hexadienyl)-4-methyl-3-(phenylseleno)methyl-5-pentenolide (20). To a solution of $(PhSe)_2CH_2$ (192 mg, 0.589 mmol) in THF (1.1 ml) was slowly added *n*-BuLi (1.61 M in hexane, 0.39 ml, 0.628 mmol) at −78°C, and the resulting solution was stirred at the same temperature for 1.5 h. After addition of HMPA (1 ml), a solution of the lactone **19** (112 mg, 0.453 mmol) in THF (0.2 ml, plus 0.1 ml rinse) was added by cannula. The mixture was stirred at −78°C for 30 min, and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with ether (×1), and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=6:1) to afford the desired product **20** as white crystals (138 mg, 73%): mp 80–82°C (ether–pentane); $[\alpha]_D^{24}$=+32.8 (*c* 0.6, $CHCl_3$); IR $\nu_{max}^{KBr\ disk}$ cm^{-1} 1728, 1578, 1478, 1439, 1375, 1256, 1080; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.9 Hz, C_{13}-C*H*$_3$), 1.14 (9H, s, *t-Bu*), 1.65 (3H, s, C_{14}-C*H*$_3$), 1.79 (3H, d, *J*=1.0 Hz, C_{15}-C*H*$_3$), 2.10 (1H, m, C_3-*H*), 1.94 (1H, m, C_4-*H*), 2.41 (1H, dd, *J*=16.2, 9.6 Hz, C_2-*H*), 2.68 (1H, dd, *J*=16.2, 6.6 Hz, C_2-*H*), 3.03 (2H, d, *J*=6.6 Hz, PhSeC*H*$_2$), 4.65 (1H, br, C_5-*H*), 5.26 (1H, t, *J*=1.3 Hz, C_9-*H*), 6.00 (1H, s, C_7-*H*), 7.27 (3H, m, Ar*H*), 7.52 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.3, 15.2, 17.9, 30.9, 32.5, 34.0, 34.3, 35.4, 37.9, 81.2, 127.4, 127.9, 129.3, 130.5, 132.0, 132.9, 133.0, 140.3, 171.7. HRMS (EI) *m*/*z* Calcd for $C_{23}H_{32}O_2Se$: 420.1567. Found: 420.1568.

Vinyl iodide (22). To a solution of the alcohol **21** (206 mg, 0.725 mmol) in CH_2Cl_2 (2.5 ml) was added triethylamine (0.2 ml, 1.43 mmol), TESC1 (0.18 ml, 1.07 mmol) and DMAP (5 mg, 0.041 mmol) at 0°C. After being stirred at 0°C for 5 min and then at room temperature for 1.5 h, the mixture was diluted with ether. The reaction mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the silyl ether.

To a solution of the silyl ether in CH_2Cl_2 (2.5 ml) was added

DIBAL (0.94 M in hexane, 2.3 ml, 2.16 mmol) at −78°C. After being stirred at −78°C for 10 min and then at −10°C for 10 min, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with ether (×1). The organic extracts were washed with water, saturated aqueous $NaHCO_3$, and brine, dried, ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=6:1) to afford the desired product **22** as a colorless oil (254 mg, 88%): $[\alpha]_D^{24}=+33.6$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368, 1456, 1414, 1379, 1264, 1240; ^1H NMR ($CDCl_3$) δ 0.56 (6H, q, *J*=8.3 Hz, $SiCH_2CH_3$), 0.84 (3H, d, *J*=6.6 Hz, C_{13}-CH_3), 0.92 (9H, t, *J*=8.3 Hz, $SiCH_2CH_3$), 1.77 (3H, s, C_{14}-CH_3), 1.88 (1H, m, C_4-*H*), 2.01 (1H, br, O*H*), 3.39–3.55 (2H, m, C_3-CH_2), 4.21 (1H, d, *J*=5.3 Hz, C_5-*H*), 6.17 (1H, d, *J*=1.0 Hz, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 4.6, 6.5, 11.6, 21.0, 39.4, 65.2, 78.1, 78.4, 149.0. Anal. Calcd for $C_{13}H_{27}IO_2Si$: C, 42.16; H, 7.35. Found: C, 42.20; H, 7.56.

(2*S*,3*R*,4*E*,6*E*)-3-trimethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienol (17) (by Suzuki coupling). 4,4-Dimethyl-2-pentyne (**11**) (0.060 ml, 0.45 mmol) was dissolved in THF (0.9 ml) and catecholborane (1 M in THF, 0.45 ml, 0.45 mmol) was added. The mixture was heated to reflux for 1.5 h and concentrated. The residue was diluted with THF (0.8 ml) and a solution of vinyl iodide **22** (83 mg, 0.208 mmol) in THF (0.2 ml, plus 0.1 ml rinse) was added by cannula. To this solution was added 2 N aqueous NaOH (0.46 ml) and $Pd(Ph_3P)_4$ (12 mg, 0.010 mmol). The reaction mixture was heated to reflux for 2 h, and quenched by the addition of 4 N aqueous NaOH (0.1 ml) and 30% aqueous H_2O_2 (0.1 ml). After being stirred at room temperature for 1 h, the mixture was extracted with ether (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane–ether=6:1) to afford the desired product **17** as a yellow oil (43 mg, 61%). ^1H and ^{13}C NMR spectra were identical with those of the authentic sample.

Ester (23). To a solution of the lactone **20** (70 mg, 0.167 mmol) in THF (1.1 ml) was added a solution of LiOH (21 mg, 0.500 mmol) in water at 0°C. The resulting mixture was stirred at 0°C for 1.5 h. After dilution with ether, the mixture was washed with 1 M aqueous $KHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the hydroxy acid.

The hydroxy acid was dissolved in DMF (1.1 ml), and $KHCO_3$ (51 mg, 0.51 mmol) was added, followed by the addition of allyl bromide (0.029 mmol, 0.335 mmol). The mixture was stirred at room temperature for 3 h. After dilution with ether, the mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the allyl ester.

The allyl ester and tripeptide unit **2** (124 mg, 0.352 mmol) were dissolved in CH_2Cl_2 (1.4 mol) and EDCI·HCl (74 mg, 0.386 mmol) was added, followed by the addition of DMAP (2 mg, 0.016 mmol) at 0°C. After being stirred at 0°C for 15 min and then at room temperature for 13 h, the mixture was diluted with ether. The mixture was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane–EtOAc=2:1∼1:1) to afford the desired product **23** as a colorless oil (104 mg, 78%): $[\alpha]_D^{24}=-79.8$ (*c* 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3324, 1732, 1686, 1638, 1478, 1414, 1377, 1246, 1188; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.85 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 0.97 (3H, d, *J*=6.6 Hz, Val-CH_3), 1.14 (9H, s, *t-Bu*), 1.33 (3H, d, *J*=6.9 Hz, Ala-CH_3), 1.66 (3H, d, *J*=1.0 Hz, C_{14}-CH_3), 1.74 (3H, d, *J*=1.0 Hz, C_{15}-CH_3), 2.08 (1H, m, C_4-*H*), 2.25 (1H, m, C_3-*H*), 2.32 (1H, m, Val-$(CH_3)_2CH$), 2.37 (1H, m, C_2-*H*), 2.67 (1H, dd, *J*=11.9, 10.6 Hz, C_2-*H*), 2.81 (1H, dd, *J*=15.8, 3.3, $PhSeCH_2$), 3.01 (3H, s, N-CH_3), 3.05 (1H, dd, *J*=11.9, 3.3 Hz, $PhSeCH_2$), 3.79 (1H, dd, *J*=18.2, 5.0 Hz, Gly-CH_2), 3.95 (1H, m, Val-α-*H*), 4.07 (1H, dd, *J*=18.1, 6.6 Hz, Gly-CH_2), 4.55 (4H, d, *J*=5.6 Hz, CH_2=CHCH_2×2), 4.65 (1H, m, Ala-α-*H*), 5.09 (1H, d, *J*=8.9 Hz, C_5-*H*), 5.26 (4H, m, CH_2=$CHCH_2$×2), 5.33 (1H, s, C_9-*H*), 5.63 (1H, br, Ala-N*H*), 5.72 (1H, s, C_7-*H*), 5.97–5.83 (2H, m, CH_2=C*H*CH_2×2), 6.50 (1H, br, Gly-N*H*), 7.24 (3H, m, Ar*H*), 7.47 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.2, 12.9, 17.8, 18.2, 18.4, 19.5, 25.3, 29.0, 30.4, 30.8, 32.6, 36.5, 36.6, 36.8, 41.0, 47.1, 62.6, 65.1, 65.6, 83.3, 117.6, 118.3, 127.1, 129.0, 129.8, 130.0, 130.2, 132.0, 132.7, 136.1, 141.1, 156.7, 168.6, 170.0, 172.1, 174.0. Anal. Calcd for $C_{41}H_{61}N_3O_8Se$: C, 61.33; H, 7.66; N, 5.23. Found: C, 61.41; H, 7.79; N, 51.4.

Protected linear peptide (25). To a solution of the ester **23** (36 mg, 0.044 mmol) in THF (0.3 ml)–water (0.2 ml) was added $NaIO_4$ (28 mg, 0.131 mmol). The mixture was stirred at room temperature for 41.5 h, and directly purified by silica gel chromatography (BW-200, hexane–EtOAc=2:1) to afford the desired product **25** as a colorless oil (27 mg 93%): $[\alpha]_D^{24}=-77.3$ (*c* 0.7, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3320, 1732, 1692, 1640, 1464, 1246, 1190; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.97 (3H, d, *J*=6.6 Hz, Val-CH_3), 1.05 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 1.12 (9H, s, *t-Bu*), 1.34 (3H, d, *J*=6.9 Hz, Ala-CH_3), 1.68 (3H, d, *J*=1.3 Hz, C_{14}-CH_3), 1.75 (3H, d, *J*=1.3 Hz, C_{15}-CH_3), 2.25 (1H, m, C_3-*H*), 2.32 (1H, m, C_4-*H*), 2.65 (1H, q, *J*=6.9 Hz, Val-$(CH_3)_2CH$), 3.02 (3H, s, N-CH_3), 3.05 (2H, s, C_2-CH_2), 3.85 (1H, dd, *J*=18.1, 5.3 Hz, Gly-CH_2), 4.09 (1H, dd, *J*=18.2, 6.3 Hz, Gly-CH_2), 4.57 (4H, m, CH_2=$CHCH_2$×2), 4.65 (2H, m, Ala-α-*H*, Val-α-*H*), 5.03 (2H, s, C_{12}-*H*), 5.35–5.14 (6H, m, CH_2=$CHCH_2$×2, C_5-*H*, C_9-*H*), 5.66 (1H, br, Ala-N*H*), 5.76 (1H, s, C_7-*H*), 5.98–5.79 (2H, m, CH_2=C*H*CH_2×2), 6.55 (1H, br, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.1, 17.8, 18.3, 18.4, 19.6, 25.4, 30.5, 30.9, 32.6, 40.4, 40.9, 41.5, 47.2, 62.7, 65.4, 65.6, 81.9, 115.8, 117.7, 118.4, 130.2, 130.3, 132.0, 132.7, 134.5, 140.8, 142.9, 155.4, 168.6, 170.0, 171.0, 174.0. HRMS (EI) *m/z* Calcd for $C_{35}H_{55}N_3O_8$: 645.3989. Found: 645.3989.

(4*S*,5*R*)-Antillatoxin (1a). To a solution of the ester **25** (26 mg, 0.040 mmol) in THF (0.4 ml) was added morpholine (0.070 ml, 0.803 mmol) and $Pd(Ph_3P)_4$ (4.6 mg, 0.004 mmol). After being stirred at room temperature for 40 min, the mixture was diluted with the phosphate buffer

(pH 6) and extracted with $CHCl_3$ (×3). The organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford the amino acid.

The amino acid was dissolved in DMF (20 ml) and cooled to 0°C. $NaHCO_3$ (24 mg, 0.286 mmol) and DPPA (0.018 ml, 0.083 mmol) were added, and the solution was stirred at 0°C for 3 days. After concentration below 40°C, the residue was diluted with EtOAc and the organic phase was washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. Preparative thin layer chromatography (0.5 mm thickness, $CHCl_3$–MeOH=20:1) followed by silica gel column chromatography (BW-200, hexane–EtOAc=1:1) afforded the desired product **1a** as a colorless oil (9 mg, 0.018 mmol, 45%): $[\alpha]_D^{25}=-55.2$ (*c* 0.24, MeOH); IR ν_{max}^{neat} cm^{-1} 3287, 1740, 1688, 1644, 1624, 1549, 1462, 1275; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.9 Hz, Val-CH_3), 0.97 (3H, d, *J*=7.6 Hz, C_{13}-CH_3), 0.98 (3H, d, *J*=6.3 Hz, Val-CH_3), 1.12 (9H, s, *t-Bu*), 1.38 (3H, d, *J*=6.6 Hz, Ala-CH_3), 1.64 (3H, d, *J*=2.0 Hz, C_{14}-CH_3), 1.74 (3H, d, *J*=1.3 Hz, C_{15}-CH_3), 2.41 (1H, m, Val-$(CH_3)_2$C*H*), 2.72 (1H, m, C_4-*H*), 2.90 (1H, d, *J*=7.3 Hz, C_2-*H*), 2.92 (3H, s, N-CH_3) 3.48 (1H, d, *J*=7.3 Hz, C_2-*H*), 3.58 (1H, dd, *J*=17.5, 1.7 Hz, Gly-CH_2), 4.16 (1H, d, *J*=10.6 Hz, Val-α-*H*), 4.71 (1H, dd, *J*=17.5, 9.6 Hz, Gly-CH_2), 5.20 (1H, s, C_9-*H*), 5.21 (3H, m, C_5-*H*, C_{12}-*H*), 5.38 (1H, m, Ala-α-H), 5.55 (1H, s, C_7-*H*), 6.41 (1H, d, *J*=9.9 Hz, Ala-N*H*), 7.99 (1H, d, *J*=8.9 Hz, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 14.7, 15.7, 18.0, 18.7, 19.4, 26.9, 28.8, 30.9, 32.6, 40.7, 41.6, 42.6, 44.5, 67.0, 80.5, 119.7, 129.8, 130.4, 131.8, 140.4, 144.6, 168.0, 168.2, 171.3, 171.7. HRMS (EI) *m/z* Calcd for $C_{28}H_{45}N_3O_5$: 503.3359. Found: 503.3362.

(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl(2*S*,3*S*,4*E*,6*E*)-3-triethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienoate (27). To a solution of the alcohol **10** (1.35 g, 8.0 mmol) in CH_2Cl_2 (24 ml) was added CMD (11.7 g, 136 mmol) in one portion. The mixture was stirred at room temperature for 4 h, and CMD was removed by filtration through a pad of Celite and washed with Et_2O. The resulting filtrate was concentrated to afford the aldehyde, which was used for the next step without further purification.

To a stirred solution of **26** (4.03 g, 8.4 mmol) in CH_2Cl_2 (80 ml) was added Et_3N (2.69 ml, 19.2 mmol). The solution was cooled to −78°C and to this was added via cannula a solution of *c*-Hex_2BOTf (0.9 M in hexane, 18.7 ml, 16.8 mmol) in CH_2Cl_2 (2 ml), which was precooled to −78°C. This resulting solution was stirred at −78°C for 2 h to complete enolization. The aldehyde was added dropwise to the solution, and the reaction mixture was stirred at −78°C for 1 h and at 0°C for 1 h. The reaction mixture was quenched by the addition of the phosphate buffer (32 ml, pH 7), followed by MeOH (80 ml) and 30% H_2O_2 (8 ml). The mixture was stirred overnight vigorously, the volatiles were removed in vacuo, and water was added. The mixture was extracted with Et_2O (×1) and the organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to afford the aldol adduct, which was used for the next step without further purification.

The aldol adduct was dissolved in $CHCl_3$ (16 ml), and 2,6-lutidine (3.48 ml, 30.0 mmol) was added, followed by the addition of TESOTf (54.3 ml, 24 mmol). The mixture was stirred at 0°C for 4 h. After dilution with Et_2O, the mixture was washed with 1 M aqueous $KHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=4:1) to afford the desired product **27** as a colorless oil (5.47 g, 90%): $[\alpha]_D^{25}=-56.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1748, 1682, 1605, 1497, 1456, 1416, 1379, 1329, 1258, 1235, 1206, 1156, 1013, 930, 907, 884, 858, 808, 749, 730; ^1H NMR ($CDCl_3$) δ 0.53 (6H, q, *J*=7.9 Hz, SiC$H_2$$CH_3$), 0.81 (3H, d, *J*=7.3 Hz, C_{13}-CH_3), 0.90 (9H, t, *J*=7.9 Hz, $SiCH_2$CH_3), 1.10 (3H, d, *J*=6.9 Hz, N CHCH_3), 1.14 (9H, s, *t-Bu*), 1.71 (3H, s, C_{14}-CH_3), 1.77 (3H, d, *J*=0.99 Hz, C_{15}-CH_3), 2.33 (3H, s, ArCH_3), 2.47 (6H, s, C_{15}-CH_3), 2.73 (1H, m, C_4-*H*), 3.96 (1H, m, NC*H*), 4.11 (1H, d, *J*=9.6 Hz, C_5-*H*), 4.42 (1H, A of AB, *J*=16.2 Hz, PhCH_2), 4.98 (1H, B of AB, *J*=16.2 Hz, PhCH_2), 5.24 (1H, s, C_9-*H*), 5.68 (1H, d, *J*=4.6 Hz, PhC*H*), 5.74 (1H, s, C_7-*H*), 6.65 (2H, d, *J*=6.9 Hz, Ar*H*), 6.93 (2H, s, Ar*H*), 7.11 (4H, m, Ar*H*), 7.25 (2H, m, Ar*H*), 7.47 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 4.8, 6.9, 11.7, 14.4, 14.4, 17.7, 22.8, 30.1, 30.9, 32.6, 44.9, 48.4, 56.8, 77.2, 81.2, 126.0, 127.2, 127.7, 128.2, 128.3, 128.4, 130.5, 132.1, 133.2, 133.3, 134.8, 138.4, 139.0, 140.3, 140.4, 142.4, 174.0. Anal. Calcd for $C_{45}H_{65}NO_5SSi$: C, 71.10; H, 8.62; N 1.84. Found: C, 70.91; H, 8.80; N 1.64.

(2*R*,3*R*,4*E*,6*E*)-3-Trimethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienol (28). To a solution of the silyl ether **27** (3.66 g, 4.8 mmol) in CH_2Cl_2 (100 ml) was added DIBAL (1.5 M in toluene, 9.7 ml, 14.5 mmol) at −78°C. After being stirred at −78°C for 30 min, the reaction mixture was quenched by the addition of 1 M aqueous $KHSO_4$. The mixture was extracted with Et_2O (×1). The organic extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=5:1) to afford the desired product **28** as a colorless oil (1.64 g, quant.): $[\alpha]_D^{25}=-8.3$ (*c* 0.85, MeOH); IR ν_{max}^{neat} cm^{-1} 3432, 1462, 1416, 1379, 1362, 1237, 1202, 1057, 1007, 909, 889, 857, 808, 739, 727; ^1H NMR ($CDCl_3$) δ 0.62 (6H, q, *J*=7.6 Hz, SiC$H_2$$CH_3$), 0.75 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 0.96 (9H, t, *J*=7.6 Hz, $SiCH_2$CH_3), 1.14 (9H, s, *t-Bu*), 1.68 (3H, d, *J*=0.99 Hz, C_{14}-CH_3), 1.79 (3H, d, *J*=0.99 Hz, C_{15}-CH_3), 1.90 (1H, m, C_4-*H*), 3.23 (1H, m, O*H*), 3.61 (2H, m, C_3-CH_2), 3.83 (1H, d, *J*=8.3 Hz, C_5-*H*), 5.25 (1H, s, C_9-*H*), 5.74 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$ δ 4.8, 6.8, 12.4, 14.2, 17.8, 31.0, 32.6, 38.3, 67.8, 58.9, 130.5, 133.3, 134.8, 140.1. Anal. Calcd for $C_{20}H_{40}O_2Si$: C, 70.52; H, 11.84. Found: C, 70.32; H, 11.69.

(2*R*,4*E*,6*E*)-1-Triethylsiloxy-3-oxo-2,4,6,8,8-pentamethyl-4,6-nonadienol (29). A mixture of **28** (130 mg, 0.38 mmol) and TBAF (1.0 M in THF, 0.95 ml, 0.95 mmol) in THF (1 ml) was stirred at 0°C for 1 h. After dilution with Et_2O, the mixture was washed with H_2O and saturated brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=5:1) to afford the diol as a colorless oil (80 mg, 93%): $[\alpha]_D^{23}-62.9$ (*c* 0.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368, 1464, 1379, 1362, 1256, 1233, 1202, 1088, 1011, 982,

891, 847, 810; ^{1}H NMR ($CDCl_3$) δ 0.75 (3H, d, J=6.9 Hz, C_{13}-CH_3), 1,14 (9H, s, *t-Bu*), 1.75 (3H, d, J=0.99 Hz, C_{14}-CH_3), 1.82 (3H, d, J=1.32 Hz, C_{15}-CH_3), 1.95 (1H, m, C_4-*H*), 2.37 (1H, br, OH), 3.01 (1H, br, OH), 3.70 (2H, m, C_3-CH_2), 3.88 (1H, br, J=8.9 Hz, C_5-*H*), 5.31 (1H, s, C_9-*H*), 5.81 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 12.3, 13.8, 17.9, 30.9, 32.5, 37.5, 68.4, 85.4, 130.5, 134.0, 134.9, 140.7. HRMS (EI) *m/z* Calcd for $C_{16}H_{26}O_2$: 226.1933. Found: 226.1950.

To a solution of the alcohol (50 mg, 0.22 mmol) in $CHCl_3$ (0.6 ml) was added triethylamine (0.034 ml, 0.24 mmol), TESCl (0.040 ml, 0.24 mmol) and DMAP (2.4 mg, 0.020 mmol) at 0°C. After being stirred at 0°C for 15 min and then at room temperature overnight, the mixture was diluted with Et_2O. The mixture was washed with 1 M aqueous $KHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the silyl ether.

To a stirred mixture of the silyl ether, *N*-methylmorpholine *N*-oxide (54 mg, 0.0.46 mmol) and powdered 4 Å molecular sieves (154 mg) in CH_3CN (1.2 ml) was added TPAP (6 mg, 0.017 mmol) in one portion at 0°C. After being stirred at 0°C for 30 min and then at room temperature for 30 min, the mixture was filtered through silica gel and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=20:1) to afford **29** as a colorless oil (61 mg, 82%): $[\alpha]_D^{23}$ −23.0 (*c* 0.9, MeOH); IR ν_{max}^{neat} cm^{-1} 1663, 1615, 1452, 1416, 1383, 1364, 1237, 1213, 1100, 1038, 1017, 810, 745; ^{1}H NMR ($CDCl_3$) δ 0.56 (6H, q, J=7.9 Hz, SiCH_2CH$_3$), 0.92 (9H, t, J=7.9 Hz, SiCH$_2$CH_3), 1.06 (3H, d, J=6.6 Hz, C_{13}-CH_3), 1,18 (9H, s, *t-Bu*), 1.91 (3H, d, J=1.3 Hz, C_{14}-CH_3), 1.94 (3H, d, J=1.3 Hz, C_{15}-CH_3), 3.52 (2H, m, C_3-*H*), 3.81 (1H, m, C_4-*H*), 5.59 (1H, s, C_9-*H*), 6.98 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 4.3, 6.4, 14.9, 17.4, 30.7, 33.1, 42.2, 66.1, 77.2, 131.1, 134.5, 145.5, 145.7, 205.9. Anal. Calcd for $C_{20}H_{38}O_2Si$: C, 70.94; H, 11.31. Found: C, 70.66; H, 11.27.

(2*S*,4*E*,6*E*)-1-Triethylsiloxy-3-oxo-2,4,6,8,8-pentamethyl-4,6-nonadienol (30). The alcohol **17** (108 mg, 0.317 mmol) was treated as described for the synthesis of **29** to afford the diol as a colorless oil (107 mg, quant.): $[\alpha]_D^{23}$=+18.3 (*c* 1.4, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368, 1464, 1379, 1362, 1254, 1233, 1202, 1178, 1116, 1088, 1036, 1013, 982, 895; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, d, J=7.3 Hz, C_{13}-CH_3), 1,15 (9H, s, *t-Bu*), 1.72 (3H, d, J=1.3 Hz, C_{14}-CH_3), 1.82 (3H, d, J=1.32 Hz, C_{15}-CH_3), 1.93 (1H, m, C_4-*H*, OH×2), 3.66 (2H, d, J=5.0 Hz, C_3-CH_2), 4.12 (1H, d, J=5.0 Hz, C_5-*H*), 5.29 (1H, s, C_9-*H*), 5.88 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 10.8, 14.6, 18.1, 31.0, 32.6, 37.9, 66.8, 77.2, 130.8, 131.1, 135.2, 140.3. HRMS (EI) *m/z* Calcd for $C_{16}H_{26}O_2$: 226.1933. Found: 226.1945.

The ester (10 mg, 0.044 mmol) was treated as described for the synthesis of **29** to afford the ketone **30** as a colorless oil (10 mg, 67%): IR, ^{1}H NMR and ^{13}C NMR spectra were identical with **29**. $[\alpha]_D^{23}$=+21.5 (*c* 0.5, MeOH). Anal. Calcd for $C_{20}H_{38}O_2Si$: C, 70.94; H, 11.31. Found: C, 70.63; H, 11.05.

Methyl (4*R*,5*R*,2*Z*,6*E*,8*E*)-5-Triethylsiloxy-4,6,8,10,10-pentamethyl-6,8-undecadienoate (31). The alcohol **27** (1.02 g, 3.00 mmol) was treated as described for the synthesis of **18** to give the ester **31** as a colorless oil (966 mg, 82%): $[\alpha]_D^{21}$=−35.8 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1727, 1654, 1458, 1437, 1408, 1377, 1362, 1223, 1194, 1175, 1130, 1102, 1075, 1034, 1007, 972, 858, 822, 741, 725; ^{1}H NMR ($CDCl_3$) δ 0.56 (6H, q, J=7.9 Hz, SiCH_2CH$_3$), 0.92 (12H, m, SiCH$_2$CH_3, C_{13}-CH_3), 1.13 (9H, s, *t-Bu*), 1.66 (3H, s, C_{14}-CH_3), 1.76 (3H, s, C_{15}-CH_3), 3.69 (3H, s, CH_3 ester), 3.76 (2H, m, C_4-*H*, C_5-*H*), 5.20 (1H, m, C_9-*H*), 5.73 (1H, s, C_2-*H*), 5.77 (1H, s, C_7-*H*), 6.17 (1H, dd, J=11.6, 9.6 Hz, C_3-*H*); ^{13}C NMR ($CDCl_3$) δ 4.9, 6.9, 13.3, 17.4, 17.8, 31.0, 32.5, 37.4, 50.9, 82.4, 118.7, 130.8, 132.1, 135.3, 139.6, 153.6, 166.8. Anal. Calcd for $C_{23}H_{42}O_2Si$: C, 70.00; H, 10.70. Found: C, 69.70; H, 10.79.

(4*R*,5*R*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1-3-hexadienyl)-4-methyl-2-pentene-5-olide (32). The ester **31** (600 mg, 1.5 mmol) was treated as described for the synthesis of **19** to afford the lactone **32** as a colorless oil (234 mg, 63%): $[\alpha]_D^{23}$=−96.4 (*c* 0.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1730, 1651, 1375, 1289, 1264, 1235, 1175, 1201, 1084, 1009, 918, 891, 847, 814, 733; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, d, J=7.3 Hz, C_{13}-CH_3), 1.13 (9H, s, *t-Bu*), 1.78 (3H, s, C_{14}-CH_3), 1.80 (3H, s, C_{15}-CH_3), 2.72 (1H, m, C_4-*H*), 4.33 (1H, d, J=11.2 Hz, C_5-*H*), 5.32 (1H, s, C_9-*H*), 5.88 (1H, s, C_2-*H*), 5.97 (1H, dd, J=5.9.9, 2.6 Hz, C_7-*H*), 6.68 (1H, dd, J=9.9, 2.6 Hz, C_3-*H*); ^{13}C NMR ($CDCl_3$) δ 12.7, 15.7, 17.6, 30.8, 31.1, 32.6, 90.7, 120.1, 129.1, 130.1, 137.5, 141.4, 151.9, 164.5. HRMS (EI) *m/z* Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1764.

Ester (34). The lactone **32** (154 mg, 0.623 mmol) was treated as described for the synthesis of **20** and **23** to afford the ester **34** as a colorless oil (77 mg, 15% in 4 steps): $[\alpha]_D^{23}$=−35.4 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3314, 1732, 1682, 1645, 1580, 1530, 1480, 1414, 1377, 1275, 1244, 1192, 1148, 1094, 1065, 1022, 994, 930, 750, 739; ^{1}H NMR ($CDCl_3$) δ 0.67 (3H, d, J=7.0 Hz, C_{13}-CH_3), 0.83 (3H, d, J=6.4 Hz, Val-CH_3), 0.97 (3H, d, J=6.4 Hz, Val-CH_3), 1.12 (9H, s, *t*-Bu), 1.33 (3H, d, J=7.0 Hz, Ala-CH_3), 1.66 (3H, d, J=1.22 Hz, C_{14}-CH_3), 1.76 (3H, d, J=1.22, C_{15}-CH_3), 2.18 (1H, m, C_4-*H*), 2.29–2.40 (2H, m, C_3-*H*, Val-(CH$_3$)C*H*), 2.46 (1H, m, C_2-CH_2), 2.78 (1H, m, C_2-CH_2), 2.86 (1H, s, PhSeCH_2), 3.02 (3H, s, N-CH_3), 3.05 (1H, dd, J=12.5, 5.8 Hz, PhSeCH_2), 3.76 (2H, dd, J=18.1, 5.3 Hz, Gly-CH_2), 3.86 (1H, dd, J=18.3, 5.5 Hz, Val-α-*H*), 4.57 (4H, m, CH$_2$=CHCH_2×2), 4.67 (1H, m, Ala-α-*H*), 4.91 (1H, d, J=9.5 Hz, C_5-*H*), 5.20–5.30 (4H, m, CH_2=CHCH$_2$×2), 5.32 (1H, d, J=1.5 Hz, C_9-*H*), 5.66 (1H, br, J=7.9 Hz, Ala-N*H*), 5.81 (1H, s, C_7-*H*), 5.84–5.95 (2H, m, CH$_2$=C*H*CH$_2$×2), 6.42 (1H, t, J=5.5 Hz, Gly-N*H*), 7.27 (3H, m, Ar*H*), 7.51 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.5, 13.0, 18.4, 18.5, 19.7, 25.6, 30.3, 30.5, 30.9, 32.6, 34.5, 34.7, 35.8, 40.9, 47.2, 62.7, 65.3, 65.6, 82.8, 117.6, 118.4, 127.1, 129.1, 129.9, 130.4, 132.2, 132.7, 133.0, 136.2, 141.2, 155.4, 168.7, 169.8, 172.4, 173.8. Anal. Calcd for $C_{41}H_{61}N_3O_8Se$·0.5EtOAc: C, 60.98; H, 7.74; N, 4.96. Found: C, 61.26; H, 7.80; N, 4.60.

Protected linear peptide (35). The ester **34** (16 mg, 0.02 mmol) was treated as described for the synthesis of **25** to give the protected linear peptide **35** as a colorless oil

(10 mg, 81%): $[\alpha]_D^{23}=-43.6$ (*c* 0.95, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 1735, 1692, 1640, 1534, 1466, 1414, 1375, 1364, 1327, 1273, 1244, 1194, 1152, 1084, 1063, 1036, 1013, 994, 930, 851, 820, 777, 756; ^1H NMR ($CDCl_3$) δ 0.83 (3H, d, *J*=6.7 Hz, Val-CH_3), 0.94 (3H, d, *J*=7.0, C_{13}-CH_3), 0.97 (3H, d, *J*=6.7, Val-CH_3), 1.13 (9H, s, *t*-Bu), 1.33 (3H, d, *J*=7.0 Hz, Ala-CH_3), 1.69 (3H, d, *J*=1.5 Hz, C_{14}-CH_3), 1.79 (3H, d, *J*=1.2 Hz, C_{15}-CH_3), 2.31 (1H, m, C_4-*H*), 2.61 (1H, m, Val-(CH_3)C*H*), 3.02 (3H, s, N-CH_3), 3.07 (2H, d, *J*=5.2 Hz, C_2-CH_2), 3.83 (1H, dd, *J*=18.1, 5.3 Hz, Gly-CH_2), 4.00 (1H, dd, *J*=18.3, 5.3 Hz, Gly-CH_2), 4.59 (6H, m, Val-α-*H*, CH_2=CHCH_2×2, Ala-α-*H*), 5.04 (3H, m, C_{12}-*H*, C_5-*H*), 5.20–5.35 (5H, m, C_9-*H*, CH_2=CHCH_2×2), 5.64 (1H, d, *J*=8.2 Hz, Ala-N*H*), 5.90 (1H, s, C_7-*H*), 5.92 (2H, m, CH_2=C*H*CH_2×2), 6.48 (1H, brt, *J*=5.48 Hz, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 12.8, 16.7, 17.8, 18.4, 18.5, 19.6, 25.5, 30.5, 30.9, 32.6, 40.6, 40.9, 41.7, 47.2, 62.7, 65.4, 65.6, 84.3, 115.3, 117.6, 118.5, 129.6, 130.3, 130.4, 132.7, 136.8, 141.3, 143.5, 155.4, 168.3, 169.8, 171.2, 173.9. HRMS (EI) *m/z* Calcd for $C_{35}H_{55}N_3O_8$: 645.3989. Found: 645.3990.

(4*R*,5*R*)-Antillatoxin (1b). The protected linear peptide **35** (18 mg, 0.027 mmol) was treated as described for the synthesis of **1a** to afford the desired product **1b** as a colorless oil (5 mg, 37%): $[\alpha]_D^{21}=-147$ (*c* 0.23, MeOH); IR ν_{max}^{neat} cm^{-1} 3281, 1738, 1692, 1646, 1553, 1260; ^1H NMR ($CDCl_3$) δ 0.86 (3H, d, *J*=6.9 Hz, Val-CH_3), 0.88 (3H, d, *J*=6.7 Hz, C_{13}-CH_3), 0.98 (3H, d, *J*=6.3 Hz, Val-CH_3), 1.12 (9H, s, *t-Bu*), 1.42 (3H, d, *J*=6.6 Hz, Ala-CH_3), 1.56 (3H, d, *J*=1.0 Hz, C_{14}-CH_3), 1.79 (3H, d, *J*=1.0 Hz, C_{15}-CH_3), 2.17 (1H, m, C_4-*H*), 2.45 (1H, m, Val-$(CH_3)_2$C*H*), 2.79 (1H, d, *J*=12.5 Hz, C_2-*H*), 2.87 (3H, s, N-CH_3), 2.97 (1H, d, *J*=13.2 Hz, C_2-*H*), 3.48 (1H, dd, *J*=18.2, 1.3 Hz, Gly-CH_2), 4.25 (1H, d, *J*=10.8 Hz, Val-α-*H*), 4.69 (1H, dd, *J*=18.2, 9.9 Hz, Gly-CH_2), 5.01 (1H, s, C_{12}-*H*), 5.06 (1H, s, C_{12}-*H*), 5.17 (1H, d, *J*=10.9 Hz, C_5-*H*), 5.30 (1H, s, C_9-*H*), 5.36 (1H, m, Ala-α-*H*), 5.94 (1H, s, C_7-*H*), 6.66 (1H, d, *J*=9.4 Hz, Ala-N*H*), 7.97 (1H, d, *J*=9.6 Hz, Gly-N*H*), ^{13}C NMR ($CDCl_3$) δ 12.4, 17.8, 18.6, 18.7, 18.9, 19.3, 26.1, 28.8, 30.9, 32.6, 39.0, 41.1, 43.1, 67.1, 83.4, 113.8, 129.2, 130.4, 137.3, 141.5, 144.8, 167.6, 167.8, 171.1, 173.2. HRMS (EI) *m/z* Calcd for $C_{28}H_{45}N_3O_5$: 503.3359. Found: 503.3362.

[4*S*,3(2*S*,3*S*)]-4-Benzyl-3-(3-hydroxy-2,4,6,8,8-pentamethyl-4,6-nonadienoyl)-2-oxazolidinone (36). The alcohol **10** (2.26 g, 13.4 mmol) was treated as described for the synthesis of **15** to afford **36** as a pale yellow oil (5.609 g, 98%): IR, ^1H NMR and ^{13}C NMR were identical with **15**. $[\alpha]_D^{26}=+19.7$ (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{24}H_{33}O_4\cdot 0.25H_2O$: C, 71.35; H, 8.36; N 3.47. Found: C, 71.52; H, 8.26; N 3.14.

Methyl (2*S*,3*S*,4*E*,6*E*)-3-Hydroxy-2,4,6,8,8-pentamethyl-4,6-nonadienoate (37). To a solution of the aldol adduct **36** (1.80 g, 4.19 mmol) in CH_2Cl_2 (40 ml) was added NaOMe (0.4 M in MeOH, 11.5 ml, 4.6 mmol) at −30°C. After being stirred for 10 min, the mixture was quenched with 1 M aqueous $KHSO_4$, and extracted with Et_2O (×2). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=6:1) to afford **37** as a colorless oil (942 mg, 88%): $[\alpha]_D^{26}=-9.1$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3475, 1740, 1658, 1458, 1437, 1377, 1362, 1348, 1256, 1200, 1165, 1121, 1169, 1040, 1017, 889, 857, 758, 712; ^1H NMR ($CDCl_3$) δ 1.14 (9H, s, *t-Bu*), 1.16 (3H, d, *J*=7.3 Hz, C_{13}-CH_3), 1.70 (3H, s, C_{14}-CH_3), 1.79 (3H, s, C_{15}-CH_3), 2.44 (1H, br, O*H*), 2.75 (1H, m, C_4-*H*), 3.68 (3H, s, CH_3 ester), 4.27 (1H, br, C_5-*H*), 5.26 (1H, s, C_9-*H*), 5.78 (1H, s, C_7-*H*); ^{13}C NMR ($CDCl_3$) δ 11.3, 13.9, 18.0, 31.0, 32.6, 43.1, 51.8, 76.6, 130.7, 131.8, 132.3, 133.1, 140.2, 176.0. HRMS (EI) *m/z* Calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1879.

(2*R*,3*S*,4*E*,6*E*)-3-Trimethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienol (38). To a solution of the alcohol **37** (850 mg, 3.34 mmol) was treated as described for the synthesis of **17** to afford the alcohol **38** as a colorless oil (1.04 g, quant.): IR, ^1H NMR and ^{13}C NMR spectra were identical with **17**. $[\alpha]_D^{24}=-1.6$ (*c* 1.1, MeOH); Anal. Calcd for $C_{20}H_{40}O_2Si$: C, 70.52; H, 11.84. Found: C, 70.21; H, 11.75.

Methyl (4*R*,5*S*,2*Z*,6E,8*E*)-5-Triethylsiloxy-4,6,8,10,10-pentamethyl-6,8-undecadienoate (39). The alcohol **38** (1.08 mg, 3.17 mmol) was treated as described for the synthesis of **18** to afford the ester **39** as a colorless oil (907 mg, 73%): IR, ^1H NMR and ^{13}C NMR spectra were identical with **18**. $[\alpha]_D^{25}=-89.3$ (*c* 0.85, $CHCl_3$); Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73. Found: C, 69.78; H, 10.55.

(4*R*,5*S*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1,3-hexadienyl)-4-methyl-2-pentene-5-olide (40). The ester **39** (237 mg, 0.70 mmol) was treated as described for the synthesis of **19** to afford the lactone **40** as a colorless oil (113 mg, 76%): IR, ^1H NMR and ^{13}C NMR were identical with **19**. $[\alpha]_D^{32}=-352.6$ (*c* 0.3, $CHCl_3$); HRMS (EI) *m/z* Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1775.

(3*R*,4*S*,5*R*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1,3-hexadienyl)-4-methyl-3-(phenylseleno)methyl-5-pentenolide (41). The lactone **40** (96 mg, 0.389 mmol) was treated as described for the synthesis of **20** to afford the selenolactone **41** as a yellow oil (110 mg, 68%): IR, ^1H NMR and ^{13}C NMR spectra were identical with **20**. $[\alpha]_D^{24}=-31.1°$ (*c* 0.6, $CHCl_3$); HRMS (EI) *m/z* Calcd for $C_{23}H_{32}O_2Se$: 420.1567. Found: 420.1568.

Ester (42). The lactone **41** (77 mg, 0.184 mmol) was treated as described for the synthesis of **23** to afford the ester **42** as a colorless oil (86 mg, 58%): $[\alpha]_D^{24}=-61.1$ (*c* 0.25, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3304, 1732, 1682, 1638, 1537, 1477, 1414, 1379, 1244, 1190, 1148, 1065, 1022, 990, 932, 891, 739; ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.85 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 0.97 (3H, d, *J*=6.6 Hz, Val-CH_3), 1.14 (9H, s, *t-Bu*), 1.32 (3H, d, *J*=6.6 Hz, Ala-CH_3), 1.66 (3H, s, C_{14}-CH_3), 1.74 (3H, s, C_{15}-CH_3), 2.07 (1H, m, C_4-*H*), 2.31–2.41 (3H, m, C_3-*H*, Val-$(CH_3)_2$C*H*, C_2-*H*), 2.67 (1H, m, C_2-*H*), 2.77 (1H, d, *J*=4.3 Hz, PhSeCH_2) 3.01 (3H, s, N-CH_3), 3.07 (1H, m, PhSeCH_2), 3.96 (3H, m, Gly-CH_2, Val-α-*H*), 4.55 (4H, m, CH_2=CHCH_2×2), 4.62 (1H, s, Ala-α-*H*), 5.09 (1H, d, *J*=8.6 Hz, C_5-*H*), 5.18–5.33 (4H, m, CH_2=CHCH_2×2), 5.34 (1H, s, C_9-*H*), 5.72 (2H, m, Ala-N*H*,

C_7-*H*), 5.85–5.95 (2H, m, CH_2=C*H*CH_2×2), 6.57 (1H, br, Gly-N*H*), 7.24 (3H, m, Ar*H*), 7.47 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.2, 13.0, 17.8, 18.3, 18.4, 19.6, 25.5, 29.2, 30.5, 30.9, 32.6, 36.6, 36.7, 36.8, 41.0, 47.2, 62.6, 65.2, 65.6, 83.3, 117.6, 118.4, 127.2, 129.1, 129.8, 130.0, 130.3, 132.0, 132.7, 136.0, 141.1, 155.4, 168.7, 170.0, 172.1, 173.9. Anal. Calcd for $C_{41}H_{61}N_3O_8Se$: C, 61.33; H, 7.66; N, 5.23. Found: C, 61.44; H, 7.70; N, 4.95.

Protected linear peptide (43). The ester **42** (21 mg, 0.026 mmol) was treated as described for the synthesis of **25** to afford the protected linear peptide **43** as a colorless oil (16 mg, quant.): $[\alpha]_D^{25}$=−82.0 (*c* 0.54, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3324, 1738, 1732, 1684, 1636, 1507, 1456, 1375, 1364, 1326, 1273, 1244, 1192, 1150, 1090, 1063, 936, 932, 777, ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.98 (3H, d, *J*=6.6 Hz, Val-CH_3), 1.04 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 1.12 (9H, s, *t-Bu*), 1.33 (3H, d, *J*=6.9 Hz, Ala-CH_3), 1.68 (3H, s, C_{14}-CH_3), 1.75 (3H, s, C_{15}-CH_3), 2.32 (1H, m, C_4-*H*), 2.65 (1H, m, Val-$(CH_3)_2$C*H*), 3.00 (3H, s, N-CH_3), 3.05 (2H, s, C_2-CH_2) 3.97 (1H, dd, *J*=18.2, 5.0 Hz, Gly-CH_2), 4.07 (1H, dd, *J*=178, 5.9 Hz, Gly-CH_2), 4.56 (4H, m, CH_2=CHCH_2×2), 4.61 (2H, m, Ala-α-*H*, Val-α-*H*), 5.02 (2H, s, C_{12}-*H*), 5.16–5.34 (6H, m, CH_2=CHCH_2×2, C_5-*H*, C_9-*H*), 5.62 (1H, br, Ala-N*H*), 5.77 (1H, s, C_7-*H*), 5.83–5.98 (2H, m, CH_2=C*H*CH_2×2), 6.45 (1H, br, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.8, 17.8, 18.3, 18.4, 19.6, 25.4, 30.5, 30.9, 32.6, 40.5, 40.9, 41.4, 47.2, 62.8, 65.4, 65.6, 81.7, 115.8, 117.7, 118.4, 130.1, 130.4, 132.0, 132.7, 134.3, 140.7, 143.0, 155.3, 168.6, 169.9, 171.0, 173.9. MS *m/z*: 645 (M^+).

(4*R*,5*S*)-Antillatoxin (1c). The protected linear peptide **43** (23 mg, 0.0356 mmol) was treated as described for the synthesis of **1a** to afford the desired product **1c** as a colorless oil (6 mg, 37%): $[\alpha]_D^{24}$=−64.8 (*c* 0.13, MeOH); IR ν_{max}^{neat} cm^{-1} 3291, 1744, 1686, 1626, 1534, 1464, 1262; ^{1}H NMR (DMSO-d_6) δ 0.76 (3H, d, *J*=6.9 Hz, Val-CH_3), 0.90 (3H, d, *J*=7.3 Hz, C_{13}-CH_3), 1.00 (3H, d, *J*=6.3 Hz, Val-CH_3), 1.11 (9H, s, *t-Bu*), 1.18 (3H, d, *J*=6.3 Hz, Ala-CH_3), 1.63 (3H, s, C_{14}-CH_3), 1.73 (3H, d, *J*=1.0 Hz, C_{15}-CH_3), 2.18–2.24 (2H, m, C_4-*H*, Val-$(CH_3)_2$C*H*), 2.64 (3H, s, N-CH_3), 2.94 (1H, s, C_2-*H*), 3.04 (1H, s, C_2-*H*), 3.67 (1H, dd, *J*=16.8, 5.0 Hz, Gly-CH_2), 3.93 (1H, d, *J*=9.6 Hz, Val-α-*H*), 4.18 (1H, dd, *J*=16.8, 6.9 Hz, Gly-CH_2), 4.64 (1H, m, Ala-α-*H*), 4.78 (1H, s, C_5-*H*), 4.94, (1H, s, C_{12}-*H*), 5.00 (1H, s, C_{12}-*H*), 5.20 (1H, s, C_9-*H*), 5.61 (1H, s, C_7-*H*), 8.00 (1H, br, Gly-N*H*), 8.35 (1H, d, *J*=8.3 Hz, Ala-N*H*); ^{13}C NMR (DMSO-d_6) δ 14.0, 15.6, 17.7, 17.9, 18.7, 27.1, 29.0, 30.8, 32.2, 40.9, 41.7, 42.2, 44.9, 64.9, 81.2, 124.9, 130.4, 130.6, 139.6, 144.7, 167.9, 169.1, 169.4, 171.4. HRMS (EI) *m/z* Calcd for $C_{28}H_{45}N_3O_5$:503.3359. Found: 503.3362.

[1*R*, 2*S*)]-2-(*N*-Benzyl-*n*-mesitylenesulfonyl)amino-1-phenyl-1-propyl(2*R*, 3*R*, 4*E*, 6*E*)-3-triethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadienoate (44). The alcohol **10** (13.5 g, 8.0 mmol) was treated as described for the synthesis of **27** to afford the aldol adduct **44** as a colorless oil (5.59 g, 92%): IR ^{1}H NMR and ^{13}C NMR spectra were identical with **27**. $[\alpha]_D^{21}$=+54.1 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{45}H_{65}NO_5SSi$: C, 71.10; H, 8.62; N 1.84. Found: C, 70.98; H, 8.65; N 1.59.

(2*S*,3*S*,4*E*,6*E*)-3-Trimethylsiloxy-2,4,6,8,8-pentamethyl-4,6-nonadioenol (45). The aldol adduct **44** (4.03 g, 5.3 mmol) was treated as described for the synthesis of **28** to afford the alcohol **45** as a pale yellow oil (1.81 g, quant.): IR ^{1}H NMR and ^{13}C NMR spectra were identical with **28**. $[\alpha]_D^{25}$=+8.8 (*c* 1.0, MeOH). Anal. Calcd. for $C_{20}H_{40}NO_2Si$: C, 70.52; H, 11.84. Found: C, 70.26; H, 11.75.

Methyl (4*S*,5*S*,2*Z*,6*E*,8*E*)-5-Triethylsiloxy-4,6,8,10,10-pentamethyl-6,8-undecadienoate (46). The alcohol **45** (788 mg, 2.30 mmol) was treated as described for the synthesis of **31** to afford the ester **46** as a colorless oil (724 mg, 80%): IR, ^{1}H NMR and ^{13}C NMR spectra were identical with **31**. $[\alpha]_D^{21}$=+34.0 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{23}H_{42}O_2Si\cdot 0.5H_2O$: C, 68.43; H, 10.74. Found: C, 68.69; H, 10.47.

(4*S*,5*S*)-5-((1*E*,3*E*)-1,3,6,6-Tetramethyl-1,3-hexadienyl)-4-methyl-2-pentene-5-olide (47). The ester **46** (600 mg, 1.5 mmol) was treated as described for the synthesis of **32** to afford the lactone **47** as a colorless oil (200 mg, 54%): IR, ^{1}H NMR and ^{13}C NMR spectra were identical with **32**. $[\alpha]_D^{23}$=+96.1 (*c* 0.4, $CHCl_3$). HRMS (EI) *m/z* Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1783.

Ester (49). The lactone **47** (50 mg, 0.20 mmol) was treated as described for the synthesis of **34** to afford the ester **49** as a colorless oil (30 mg, 18%): $[\alpha]_D^{23}$=−43.6 (*c* 0.33, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3325, 3090, 1732, 1684, 1651, 1522, 1478, 1456, 1418, 1377, 1275, 1244, 1190, 1148, 1065, 1022, 995, 930, 779, 739; ^{1}H NMR ($CDCl_3$) δ 0.66 (3H, d, *J*=6.9 Hz, C_{13}-CH_3), 0.82 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.96 (3H, d, *J*=6.3 Hz, Val-CH_3), 1.12 (9H, s, *t-Bu*), 1.30 (3H, d, *J*=6.1 Hz, Ala-CH_3), 1.66 (3H, s, C_{14}-CH_3), 1.75 (3H, s, C_{15}-CH_3, 2.16 (1H, m, C4-*H*), 2.28–2.46 (3H, m, C3-*H*, Val-(CH_3)C*H*, C_2-CH_2), 2.75–2.84 (2H, m, C_2-*H*, PhSeCH_2), 2.98 (3H, s, N-CH_3), 3.02 (1H, m, PhSeCH_2), 3.50 (2H, dd, *J*=14.0, 4.1 Hz, Gly-CH_2), 4.01 (1H, dd, *J*=18.1, 6.9 Hz, Val-α-*H*), 4.53 (4H, m, CH_2=CHCH_2×2), 4.62 (1H, m, Ala-α-*H*), 4.88 (1H, d, *J*=10.2 Hz, C_5-*H*), 5.19–5.34 (5H, m, CH_2=CHCH_2×2, C_9-*H*), 5.63 (1H, d, *J*=7.9 Hz, Ala-N*H*), 5.81 (1H, s, C_7-*H*), 5.83–5.96 (2H, m, CH_2=C*H*CH_2×2), 6.42 (1H, t, *J*=5.3 Hz, Gly-N*H*), 7.27 (3H, m, Ar*H*), 7.51 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 10.3, 12.9, 17.8, 18.4, 19.6, 25.3, 30.3, 30.9, 31.5, 32.6, 34.3, 34.5, 35.8, 40.7, 47.2, 62.5, 65.4, 65.6, 82.7, 117.6, 118.4, 127.1, 129.7, 129.9, 130.3, 132.1, 132.7, 133.0, 136.4, 141.1, 155.4, 168.7, 169.8, 172.5, 173.8. Anal. Calcd for $C_{41}H_{61}N_3O_8Se\cdot 0.5EtOAc$: C, 60.98; H, 7.74; N, 4.96. Found: C, 61.26; H, 7.80; N, 4.16.

Protected linear peptide (50). The ester **49** (20 mg, 0.025 mmol) was treated as described for the synthesis of **35** to afford the protected linear peptide **50** as a colorless oil (12 mg, 80%): $[\alpha]_D^{23}$=−52.4 (*c* 1.26 $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3325, 3090, 1735, 1686, 1640, 1526, 1466, 1414, 1380, 1367, 1333, 1282, 1242, 1192, 1152, 1063, 994, 930; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, d, *J*=6.6 Hz, Val-CH_3), 0.95 (6H, m, C_{13}-CH_3, Val-CH_3), 1.13 (9H, s, *t*-Bu), 1.32 (3H, d, *J*=6.9 Hz, Ala-CH_3), 1.68 (3H, d, *J*=0.99 Hz, C_{14}-CH_3), 1.78 (3H, d, *J*=0.99 Hz, C_{15}-CH_3), 2.30 (1H, m, C_4-*H*), 2.59 (1H, m, Val-(CH_3)C*H*), 3.00 (3H, s, N-CH_3), 3.05 (2H, m,

C_2-C*H*$_2$), 3.82 (1H, dd, *J*=18.2, 5.3 Hz, Gly-C*H*$_2$), 4.00 (1H, dd, *J*=180, 6.1 Hz, Gly-C*H*$_2$), 4.58 (6H, m, Val-α-*H*, CH_2=CHC*H*$_2$×2, Ala-α-*H*), 5.03 (3H, m, C_{12}-*H*, C_5-*H*), 5.18–5.36 (5H, m, C_9-*H*, C*H*$_2$=CHCH$_2$×2), 5.64 (1H, d, *J*=8.3 Hz, Ala-N*H*), 5.90 (3H, m, C_7-*H*, CH_2=C*H*$_2$×2), 6.51 (1H, m, Gly-N*H*); ^{13}C NMR ($CDCl_3$) δ 12.7, 16.7, 17.8, 19.6, 25.5, 30.4, 30.9, 32.6, 40.9, 41.8, 47.2, 62.6, 65.4, 65.6, 84.1, 115.3, 117.6, 118.5, 129.5, 130.4, 132.1, 136.8, 141.2, 143.6, 155.4, 168.3, 169.8, 171.2, 173.9. MS *m*/*z*: 645 (M^+).

(4*S*,5*S*)-Antillatoxin (1d). The protected linear peptide **50** (8 mg, 0.012 mmol) was treated as described for the synthesis of **1b** to afford the desired product **1d** as a colorless oil (2 mg, 32%): $[\alpha]_D^{25}$=−8.7 (*c* 0.1, MeOH); IR ν_{max}^{neat} cm^{-1} 3304, 1744, 1682, 1622, 1547, 1538, 1471, 1464, 1456, 1446, 1412, 1375, 1361, 1335, 1271, 1175, 1121, 1075, 1013, 974, 906, 754; ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, d, *J*=7.0 Hz, Val-C*H*$_3$), 0.90 (3H, d, *J*=7.0 Hz, C_{13}-C*H*$_3$), 0.99 (3H, d, *J*=6.7 Hz, C_4-*H*), 1.14 (9H, s, *t-Bu*), 1.38 (3H, d, *J*=6.7 Hz, Ala-C*H*$_3$), 1.78 (3H, s, C_{14}-C*H*$_3$), 1.88 (3H, s, C_{15}-C*H*$_3$), 2.37 (1H, m, Val-(CH$_3$)$_2$C*H*), 2.40 (1H, m, Val-C*H*$_3$), 2.86 (3H, s, N-C*H*$_3$), 3.00 (1H, m, C_2-*H*), 3.15 (1H, m, C_2-*H*), 3.94 (1H, dd, *J*=10.4, 7.3 Hz, Gly-2C*H*$_2$), 4.03 (1H, dd, *J*=17.4, 4.6 Hz, Val-α-*H*), 4.52 (1H, d, *J*=11.3 Hz, Gly-C*H*$_2$), 4.89 (1H, s, C_{12}-*H*), 4.93 (1H, s, C_9-*H*), 5.21 (3H, m, C_5-*H*, C_{12}-C*H*$_2$), 5.32 (1H, m, Ala-α-*H*), 6.01 (1H, s, C_7-*H*), 6.31 (1H, d, *J*=10.1 Hz, Ala-N*H*), 7.54 (1H, br, Gly-N*H*), ^{13}C NMR ($CDCl_3$) δ 12.9, 17.8, 18.3, 18.5, 19.3, 26.5, 29.1, 29.7, 30.9, 32.6, 40.6, 42.9, 43.2, 43.5, 65.9, 83.7, 105.3, 129.4, 130.5, 136.8, 141.3, 145.9, 166.5, 168.2, 171.6, 172.7. HRMS (EI) *m*/*z* Calcd for $C_{28}H_{45}N_3O_5$: 503.3359. Found: 503.3358.

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23. Although we attempted the macrocyclization at the other sites as shown in Fig. 4 below, the desired cyclized products could not be obtained.

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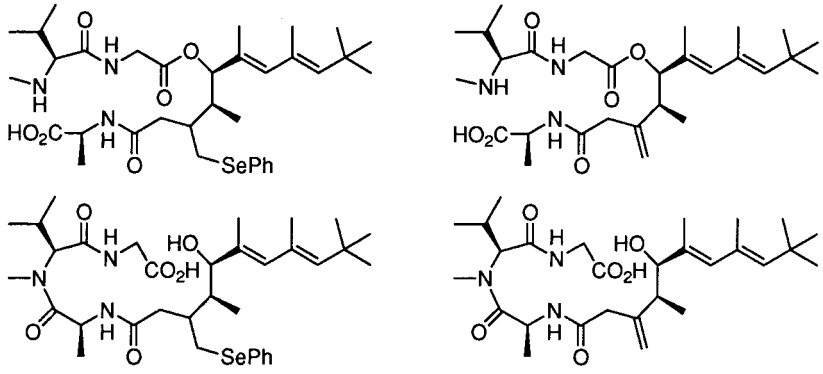

Figure 4. Attempted macrocyclization.